Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Evidence Assessment Group Report

Produced by Newcastle University

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Report key: Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Abbreviations

AEs	Adverse events
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
AUC	Area under the curve
BIC	Bayesian information criterion
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEACs	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CrI	Credible interval
CS	Company submission
CUA	Cost utility analysis
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG Performance Status
EGFR	Epidermal growth factor receptor
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	The EORTC Core Quality of Life Questionnaire
GBP	Pounds sterling
GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility values

HTA	Health technology assessment
IC	Investigator’s choice
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IMAEs	Immune-mediated adverse events
IO/IOs	Immunotherapy/immunotherapies
ITT	Intention-to-treat
IV	Intra-venous
MeSH	Medical Subject Headings
MHRA	The Medicines and Healthcare products Regulatory Agency
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBAC	The Pharmaceutical Benefits Advisory Committee
PD	Progressed Disease
PD-L1	Programmed death-ligand 1
PF	Progression-free
PfC	Points for clarification

PFS	Progression-free survival
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
Q6W	Every six weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RoB	Risk of bias
ROS	Proto-oncogene tyrosine-protein kinase
ROS-1	ROS proto-oncogene 1
SAEs	Severe adverse events
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
TA	Technology appraisal
TAR	Technology assessment reviews
TEAEs	Treatment emergent adverse events
ToT	Time on treatment
TTD	Time to death
UK	United Kingdom

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 presents the model outcomes. Section 1.3 summarises all key issues identified by the EAG relating to clinical effectiveness and cost-effectiveness. Section 1.4 summarises the EAG's preferred assumptions and ICERs.

Further detail regarding key and non-key issues are described in the main EAG Report (Sections 2 to 6).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of EAG's key issues

Issue number	Brief summary of issue	Report section(s)
1	The population who would be eligible to receive cemiplimab + chemotherapy is a subset of the NICE scope	2.1
2	The comparator included in the company's decision problem does not reflect all of the treatments in the NICE scope and clinical pathways for the population of interest	2.2
3	Uncertainty surrounding the transitivity assumption in the NMA	3.3.3
4	Uncertainty in the assumptions regarding treatment discontinuation	4.2.4
5	Uncertainty in the treatment waning assumptions made in the economic model	4.2.5
Abbreviations: EAG = Evidence Assessment Group; NMA = network meta-analysis		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. A technology is considered absolutely dominant when it improves quality of life (measured in QALYs gained) and reduces costs (measured in £GBP) relative to its best alternative treatment.

Overall, in the company economic model (CEM) the technology is modelled to affect QALYs by:

- Increasing overall survival (OS)

- Decreasing pre-progression survival time
- Increasing post-progression survival time
- Reducing the number of grade 3+ adverse events (AEs)

Overall, in the CEM the technology is modelled to affect costs by:

- Modelling greater Time on Treatment (ToT) for cemiplimab than for pembrolizumab (in scenario 4 in the CS and in the EAG base case) increases drug acquisition costs
- Increasing total disease management costs (made up of pre-progression, progressive disease and terminal care)
- Reducing the number of grade 3+ AEs

The modelling assumptions that have the greatest effect on the ICER are:

- Choice of parametric survival model for OS: In the company base-case, the company use a log-logistic distribution for the OS chemotherapy reference curve. Using alternative distributions, such as gamma and generalized gamma, decreases the incremental QALY gain for cemiplimab + chemotherapy.
- Treatment discontinuation: In the company base-case, the company assume that ToT is equal to progression free survival (PFS). Estimating ToT through application of a PFS versus ToT hazard ratio (HR) decreases the treatment costs for pembrolizumab + chemotherapy.
- Treatment waning assumption: In the company base-case, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which there an “immediate” waning, in which the estimated hazard of death is assumed to be equal to chemotherapy at five years for both PFS and OS. Using a “gradual” waning decreases the incremental QALY gain for cemiplimab + chemotherapy.
- Utilities for the progression-free (PF) and progressed-disease (PD) health states: In the company base-case, the company use estimates from the EMPOWER-Lung 3 trial[1], mapped to the EQ-5D-3L from the EORTC-QLQ C30. Using alternative utility values previously used in NICE submissions in this clinical area decrease the incremental QALY gain for cemiplimab + chemotherapy.

1.3 Description of the EAG's key clinical and economic issues

Table 1.2: Key issue 1: The population who would be eligible to receive cemiplimab + chemotherapy is a subset of the NICE scope.

Report section	Section 2.1
Description of issue and why the EAG has identified it as important	The company's decision problem is aligned with the population in the NICE scope. However, the sub-groups within this population who would be eligible to receive cemiplimab + chemotherapy are: • Patients with NSCLC, PD-L1 1-100%, no targetable mutations, non-squamous sub-group who are not contraindicated to receive IO + chemotherapy • Patients with NSCLC, PD-L1 1-49%, no targetable mutations, squamous sub-group who are not contraindicated to receive IO + chemotherapy • Patients with NSCLC, PD-L1 ≥50%, no targetable mutations, squamous sub-group where urgent clinical intervention is needed Patients with PD-L1 ≥50% in the squamous sub-group who do not require urgent clinical intervention, as well as patients from other subgroups who are contraindicated to IO + chemotherapy would therefore be ineligible for cemiplimab + chemotherapy.
What alternative approach has the EAG suggested?	None. The EAG note that the company provided evidence for the effectiveness of cemiplimab + chemotherapy in patients who would otherwise have received pembrolizumab + chemotherapy.
What is the expected effect on the cost effectiveness estimates?	There is only cost effectiveness evidence for patients who would otherwise have received pembrolizumab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	None

Report section	Section 2.1
Abbreviations: NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; EAG = evidence assessment group; IO = immunotherapy	

Table 1.3: Key issue 2: The comparator included in the company's decision problem does not reflect all of the treatments in the NICE scope and clinical pathways for the population of interest

Report section	Section 2.2
Description of issue and why the EAG has identified it as important	The company only included one comparator (pembrolizumab + chemotherapy) in their decision problem, despite various other treatment options being available in the NICE scope and clinical pathways for the population of interest.
What alternative approach has the EAG suggested?	The clinical advisor to the EAG confirmed that pembrolizumab + chemotherapy is the only suitable comparator for cemiplimab + chemotherapy, as both treatments would only be offered to patients who are not contraindicated to IO + chemotherapy and to patients with PD-L1 ≥50%, squamous histology who require urgent clinical intervention. As such, the EAG does not suggest an alternative approach in terms of the comparators against which cemiplimab + chemotherapy should be compared.
What is the expected effect on the cost effectiveness estimates?	There is only evidence for the cost-effectiveness of cemiplimab + chemotherapy compared to pembrolizumab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	None.
Abbreviations: NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; EAG = Evidence Assessment Group; IO = immunotherapy	

Table 1.4: Key issue 3: Uncertainty surrounding the transitivity assumption in the NMA

Report section	Section 3.3.3
Description of issue and why the EAG has identified it as important	The company reported that the difference in effect modifier trial characteristics across trials in the NMA was not known and the potential for bias related to this could not be assessed. In particular, the percentage of patients receiving subsequent immunotherapy in the chemotherapy control arm

Report section	Section 3.3.3
	of the KEYNOTE studies investigating pembrolizumab combination therapy was not reported at the key time point.
What alternative approach has the EAG suggested?	There is no alternative approach that can be taken in this submission.
What is the expected effect on the cost effectiveness estimates?	The effect is unknown. While the percentage of patients receiving cross-over treatment at the relevant timepoint was not reported in the KEYNOTE studies, roughly 41-42% had pembrolizumab crossover treatment following chemotherapy at 5 years in KEYNOTE-189 and KEYNOTE-407. If the percentage receiving subsequent immunotherapy treatment were higher in the chemotherapy control arms of the pembrolizumab trials than in the cemiplimab EMPOWER trial, this would likely favour cemiplimab for the OS outcome. Were that the case, the incremental QALYs for cemiplimab would be lower and cemiplimab would likely be less cost-effective than in the base case. The potential for bias associated with other effect modifiers is unknown.
What additional evidence or analyses might help to resolve this key issue?	The authors of the studies included in the NMA could be contacted to see if the relevant information exists (i.e. baseline characteristics between groups for patients with PD-L1 ≥1) and whether they could provide the information. Individual patient data across included studies in the NMA would be required to try to adjust for any subsequent treatment discrepancies.
Abbreviations: EAG = Evidence Assessment Group; NMA = network meta-analysis	

Table 1.5: Key issue 4: Uncertainty in the assumptions regarding treatment discontinuation

Report section	Section 4.2.4
Description of issue and why the EAG has identified it as important	In the base case analysis, the company assumed that the Time on Treatment (ToT) was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, guided by an advisory board meeting where advisors were cautious about concluding discrepancies between cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms. The EAG notes that assuming that ToT is equal to PFS will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy.
What alternative approach has the EAG suggested?	For consistency with the effectiveness estimates, either the ToT estimates should be estimated from the respective clinical trials (EMPOWER-Lung 3[1] and KEYNOTE-407) as

Report section	Section 4.2.4
	well as effectiveness, or instead both effectiveness and ToT should be assumed to be equal. In the EAG base case, the former approach is taken: the hazard rates of ToT from EMPOWER-Lung 3[1] and KEYNOTE-407 are used to estimate time on treatment.
What is the expected effect on the cost effectiveness estimates?	In Scenario 4 of the company's scenario analyses, the company used the hazard rates (taken from EMPOWER-Lung 3[1] and KEYNOTE-407) to PFS to estimate time on treatment. The incremental costs changed from [redacted] in in the company base case to [redacted], decreasing the cost-effectiveness of cemiplimab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	Further evidence that ToT beyond PFS does not affect OS in the relevant population treated with cemiplimab + chemotherapy would reduce the level of uncertainty regarding this issue.
Abbreviations: EAG = Evidence Assessment Group; QALY = quality-adjusted life year; ToT = Time on Treatment; PFS = progression-free survival; OS = overall; survival	

Table 1.6: Key issue 5: Uncertainty in the assumptions regarding treatment waning

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	In the CEM, the company assumed that there was an "immediate" waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. The EAG is concerned that applying waning on this "immediate" basis does not reflect the mechanism of action of IOs and lacks face validity.
What alternative approach has the EAG suggested?	As part of the EAG base case, the EAG has included a "gradual" waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy beginning at 24 months (in line with the stopping rule for both treatments) and ending at 5 years.
What is the expected effect on the cost effectiveness estimates?	Assuming a "gradual" waning of the treatment effect rather than an "immediate" waning reduces the incremental QALYs for cemiplimab + chemotherapy from [redacted] in the company base case to [redacted], thus decreasing the cost-effectiveness of cemiplimab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on the level of attenuation of treatment effects over time for cemiplimab would help to resolve this uncertainty.
Abbreviations: EAG = Evidence Assessment Group; QALY = quality-adjusted life year; CEM = cost-effectiveness model; IOs = immunotherapies	

1.4 Summary of the EAG's preferred assumptions and ICER

Three changes were made from the company's base-case to the EAG base-case.

In the company base-case, the company assume that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. In the EAG base-case, the HRs of ToT estimated from EMPOWER-Lung 3[1] for cemiplimab + chemotherapy and KEYNOTE-407 and KEYNOTE-189 for pembrolizumab are used. This aligns with Scenario 4 from the CS.

In the company base case, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which the estimated hazard of both disease progression and death is assumed to be equal to chemotherapy at five years for both PFS and OS. In the EAG base, a gradual linear waning effect for both PFS and OS starting at 24 months (in line with the stopping rule for both cemiplimab and pembrolizumab) and ending at 60 months is used, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed to be equal to the hazard for chemotherapy.

In the company base case, treatment-specific AE profiles are used, despite the chemotherapy backbone regime being assumed to be the same across treatments. In the EAG base, the AE profile for pembrolizumab + chemotherapy has been applied to both treatment arms.

The probabilistic results from the company and EAG base-case are shown in

Table 1.7. Selected results from the company and EAG's deterministic scenario analysis are shown in

Table 1.8.

Table 1.7 Probabilistic results from company and EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Probabilistic					
Cemiplimab + chemo	[redacted]	[redacted]	-	-	-
Pembrolizumab + chemo	£126,224	2.16	[redacted]	[redacted]	Dominating
EAG base-case – Probabilistic					
Cemiplimab + chemo	[redacted]	[redacted]			
Pembrolizumab + chemo	£116,595	2.11	[redacted]	[redacted]	Dominating
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

Table 1.8: Selected results from company and EAG's deterministic scenario analysis

Scenario	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	**N/A**	[redacted]	[redacted]	Dominating
CS 2	OS reference and two-step NMA (log-logistic)	Alternative OS reference and two-step NMA (generalised gamma)	[redacted]	[redacted]	Dominating
CS 3	PFS 2-step NMA (log-logistic)	PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS	[redacted]	[redacted]	Dominating
CS 5	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Waning of treatment effect applied to PFS/OS from 36 months	[redacted]	[redacted]	Dominating
CS 8	Health state utility values (EMPOWER-Lung 3 trial, EORTC to EQ-5D-5L mapping (UK tariff, modelled average)	Alternative health state utility values (NICE TA584 atezo+bev+chemo non-squamous IMpower 150 utilities using UK tariff)	[redacted]	[redacted]	Dominating
CS 10	Discount applied to pembrolizumab list price is 0%	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	[redacted]	[redacted]	[redacted]
CS 11	Discount applied to pembrolizumab list price is 0% in cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	[redacted]	[redacted]	Increased cost in cost-comparison analysis

CS 17	AE costs in the pembrolizumab + chemotherapy arm assumed equal to the EMPOWER-Lung 3 data in the cost-comparison analysis	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis (instead of assuming equal to EMPOWER-Lung 3)	[redacted]	[redacted]	Cost saving in cost-comparison analysis
EAG 9	OS reference and 2-step NMA (log-logistic)	OS reference and 2-step NMA (gamma)	[redacted]	[redacted]	Dominating
EAG 10	PFS and OS reference and 2-step NMA (log-logistic)	Generalized gamma distribution for PFS + gamma distribution for OS	[redacted]	[redacted]	Dominating
EAG 11	PFS/OS utilities from EMPOWER-Lung 3 trial, mapped from EORTC to EQ-5D-5L	Alternative utility values for PFS/OS from Nafees et al 2008)	[redacted]	[redacted]	Dominating
Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year					

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the EAG's critique of the company's decision problem is presented in Table 2.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC, which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations	As per scope	N/A	**Key issue 1** Cemiplimab + chemotherapy would not be suitable for the whole population defined in the NICE scope. See section 2.1 for further details.
Intervention	Cemiplimab with platinum-based chemotherapy	As per scope	N/A	**Appropriate** As per the NICE scope
Comparator(s)	For people with squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells:	For people with squamous and non-squamous NSCLC whose tumours express	Regeneron considers pembrolizumab + chemotherapy (which has >80% market share among NICE-recommended immunotherapy (IO) + chemotherapy	**Key issue 2** The company included only one comparator from the NICE scope, namely pembrolizumab + chemotherapy, in their decision

	• Platinum doublet chemotherapy • Pembrolizumab with carboplatin and paclitaxel For people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Platinum doublet chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (for people in need of urgent clinical intervention) For people with non-squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Atezolizumab with bevacizumab,	PD-L1 on greater than 1% of tumour cells: Pembrolizumab + chemotherapy per NHS England commissioning policies[2]	options across histologies and PD-L1 expression levels ≥1%)[3] to be the only relevant comparator for this appraisal: Feedback from UK clinical expert lung oncologists consulted during development of this submission confirmed that patients offered IO + chemotherapy comprise a patient group who are clinically distinct from those who would typically be offered chemotherapy alone because they are not considered suitable for IO, or from those who would typically be offered an IO monotherapy instead of in combination with chemotherapy. The only other NICE-recommended IO given in combination with chemotherapy is atezolizumab (TA584), which is available for use only in people with non-squamous disease and PD-L1 1-49%, and is not commonly used in UK clinical practice (having approximately 8% of market share in that population)[3] UK clinical expert lung oncologists have confirmed that pembrolizumab	problem, despite various other treatment options being available (CS Table 1, Section B.1.1, pp.12-13).[4] See section 2.2 for further details.

	carboplatin and paclitaxel • Pemetrexed with platinum doublet chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pemetrexed with platinum doublet chemotherapy		+ chemotherapy is the relevant comparator that would be displaced by use of cemiplimab + chemotherapy Overall, cemiplimab + chemotherapy will primarily act as an alternative to the current standard of care for the first-line treatment of patients in the PD-L1 ≥1%, any histology population for which it is licensed (i.e., pembrolizumab + chemotherapy)	
Outcomes	Progression-free survival (PFS) Response rates Overall survival (OS) Adverse effects of treatment Health-related quality of life	As per scope	N/A	**Appropriate** There original primary outcome reported in the protocol[1] for EMPOWER-Lung 3 trial was PFS, as opposed to OS. This was justified by the company as OS could be confounded by subsequent treatments people received whose cancer progressed. However, OS was the primary outcome that was

				reported in the EMPOWER-Lung 3 trial (CS Table 5, Section B.2.3.1, p.37).[4] The company reported results for both outcomes, therefore the EAG does not consider this to be a key issue.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	A cost-comparison analysis (assuming equivalent clinical outcomes) is included as an alternative base case alongside a cost-utility analysis.	A key challenge associated with conducting a cost-utility analysis to address the relevant decision problem on the cost-effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is the lack of head-to-head RCT evidence. As expected, there were limitations in conducting the NMA (due to inherent limitations in the evidence base and a lack of published data for the relevant comparator), and the results are associated with uncertainty as reflected in wide credible intervals. However, all the available evidence from the trial data, previously published NMA, and the Company NMA points to a conclusion of similar efficacy. This view is shared by UK clinical experts	**Some concerns** The EAG has several concerns regarding the economic analysis, including key issues relating to treatment discontinuation and treating waning assumptions. See Section 4 for further details.

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		experienced in the use of IO therapy in NSCLC, and by CADTH and PBAC. On this basis, a cost-utility analysis has been provided per the NICE scope and reference case, but a cost comparison analysis has also been provided to facilitate pragmatic decision-making. This pragmatic cost comparison approach was accepted previously by NICE (e.g. in TA705) and by both CADTH and PBAC. As described in more detail in Section B.3, Regeneron believes that currently, the justification for modelling equivalent efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy is stronger than the justification for modelling any differences in efficacy: • Cemiplimab and pembrolizumab have the same mechanism of action • There is no published evidence suggesting differences in OS or PFS between cemiplimab and pembrolizumab	

			• Only cemiplimab + chemotherapy and pembrolizumab + chemotherapy have and NCCN 'preferred' recommendation in advanced/metastatic NSCLC • UK clinical expert lung oncologists noted similarity in efficacy between the two treatments As stated above, a pragmatic cost-comparison approach has previously been accepted by other international HTA bodies.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Histology • PD-L1 status • Disease stage • Newly diagnosed or recurrent after surgery metastatic disease	Four subgroups will be considered, based on histology and PD-L1 levels, to reflect the current UK treatment pathway: Squamous, PD-L1 1-49% Squamous, PD-L1 ≥50%	The submission will not include subgroup analyses by disease stage or by newly diagnosed or recurrent after surgery metastatic disease for the following reasons: Disease stage In the UK, the Blueteq protocol (i.e. NHS England commissioning policy) permits treatment of patients with locally advanced NSCLC who are not candidates for definitive chemoradiation with pembrolizumab, despite pembrolizumab not having a marketing authorisation in locally	**Some concerns** The company did not undertake sub-group analyses by disease stage. See section 2.3 for further details.

		Non-squamous, PD-L1 1-49% Non-squamous, PD-L1 ≥50%	advanced disease.[2] These patients are therefore managed in the same way as those with metastatic disease, so subgroup analysis by disease stage lacks relevance to UK clinical practice and treatment decisions. Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs would be expected to be meaningfully different for patients with locally advanced disease (not eligible for definitive chemoradiation) versus metastatic disease. Although subgroup analysis by disease stage was planned in the overall population of the EMPOWER-Lung 3 RCT, the small number of patients in the study who were in the licensed population (i.e. PD-L1 ≥1%) with locally advanced NSCLC precludes robust subgroup analysis. Newly diagnosed or recurrent after surgery metastatic disease	

			Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs would be expected to be meaningfully different for people who have versus those who have not undergone prior surgery for NSCLC.	

Source: CS Section B.1.1, Table 1, pages 10-14.[4] PfCs response[5]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PfC = points for clarification; QALY = quality-adjusted life year; NSCLS = non-small cell lung cancer; PD-L1 = Programmed death-ligand 1; IO = immunotherapy; OS= overall survival; PFS= progression free survival; NMA = network meta-analysis; RCT = randomised controlled trial; IV = intravenous; EGFR = epidermal growth factor receptor; ALK = Anaplastic lymphoma kinase; ROS = Proto-oncogene tyrosine-protein kinase; TA = technology appraisal; Standard of Care (SoC); CADTH = Canadian Agency for Drugs and Technologies in Health; PBAC = The Pharmaceutical Benefits Advisory Committee; UK = United Kingdom; HTA = health technology assessment; NCCN = National Comprehensive Cancer Network

2.1 Population

In their decision problem, the company aligned the population of interest with the NICE scope, namely: *adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC, which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations*. However, the company focused on one comparator from the NICE scope, namely pembrolizumab + chemotherapy, despite multiple alternative treatments being available. This was justified by the company as being due to clinical differences between patients who are eligible to receive IO + chemotherapy versus IO or chemotherapy alone (CS Table 1, Section B.1.1, p.10).[4] The EAG asked the company to clarify which clinical characteristics make people unsuitable for IO + chemotherapy as this represents a subset of patients within the NICE scope who would be ineligible to receive cemiplimab + chemotherapy (PfC A4).[5] The company responded that reasons why some patients are not selected to receive IO + chemotherapy include increased age, comorbidity burden and patient preference (i.e., avoiding side-effects) (PfC A4).[5] The clinical advisor to the EAG agreed with this. The EAG's clinical advisor also explained that for patients in the PD-L1 ≥50%, squamous sub-group, IO monotherapy would be offered as the first line treatment, with chemotherapy being a second line treatment unless urgent clinical intervention is needed; for example, in the case of a rapidly progressing cancer an IO + chemotherapy would be offered as the first line treatment. Based on this, the EAG concludes that cemiplimab + chemotherapy is suitable for patients who would otherwise have been offered pembrolizumab + chemotherapy and the following population sub-groups would not be eligible to receive cemiplimab + chemotherapy:

- Patients who are contraindicated to IO + chemotherapy
- Patients with PD-L1 ≥50% in the squamous sub-group who do not require urgent clinical intervention

2.2 Comparators

The company's decision to focus on one comparator (pembrolizumab +chemotherapy) does not reflect the first line treatments from the NICE scope or clinical pathways for the population of interest, which include a more comprehensive range of treatment options. Data comparing clinical effectiveness, quality of life and adverse events between all comparators in the NICE clinical pathways would enable the EAG to better understand the benefits and harms associated with different treatments. The EAG asked the company to clarify why alternative comparators were excluded from their analyses (PfC A4).[5] The company responded that cemiplimab + chemotherapy represents an alternative treatment option that is suitable for people who would otherwise have received pembrolizumab + chemotherapy (PFC A4).[5] The clinical advisor to the EAG agreed that pembrolizumab + chemotherapy is the relevant comparator for cemiplimab + chemotherapy. The EAG concludes that pembrolizumab + chemotherapy is the recommended current practice in the NHS for the population targeted for cemiplimab + chemotherapy in this evidence submission. While a full incremental cost-effectiveness analysis might include another comparator, pembrolizumab + chemotherapy is the most important comparator in the context.

2.3 Subgroups to be considered

The population in the NICE scope are people with stages IIIB/C and IV disease; however, participants in the EMPOWER-Lung 3 trial were predominantly people with stage IV disease (n=397 in the ITT population (PD-L1 any level); n=280 in the MHRA label population (PD-L1≥1%)) compared to people with stage IIIB/C disease (n=69 in the ITT population (PD-L1 any level); n= 47 in the MHRA label population (PD-L1≥1%)), equating to approximately 85% of people within the sample with stage IV disease (CS Table 6, Section B.2.3.2, p.41).[4] The company did not undertake sub-group analysis by disease stage in the EMPOWER-Lung 3 trial in their submission. The company stated that clinical experts advised that the effectiveness of cemiplimab + chemotherapy is unlikely to vary in relation to disease stage, therefore sub-group analysis by disease stage was not required. The company also noted that the sample size of patients in the PD-L1 population with stage IIIB/C disease was too small for robust analyses by disease stage to be undertaken (CS Table 1, Section B.1.1, pp.13-14).[4] The clinical advisor to the EAG was unable to comment on differences in clinical effectiveness between people with stages IIIB/C and IV disease. However, it was noted that a sample comprising a greater number of people with stage IIIB/C disease may result in increased treatment costs due to the longer survival on average of this population sub-group compared to people with stage IV disease. Regarding the justification for not undertaking sub-group analyses by disease stage, however, the clinical advisor to the EAG agreed that the small sample size for the stage IIIB/C participants would undermine the meaningfulness of results of sub-group analyses by disease stage. Furthermore, sub-group analysis by disease stage was not planned in the protocol for the EMPOWER-Lung 3 trial.[1]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) conducted to identify evidence on the effectiveness and safety of cemiplimab + chemotherapy for treatment of NSCLC. A summary of the EAG's critique is presented in Table 3.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 3.1: Summary of the EAG's critique of the clinical effectiveness systematic literature review

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D, Section D1.1, p.33	**Appropriate** The EAG is satisfied that the company used an appropriate range of data sources.
Search strategies	Appendix D, Section D1.1, p.33-49	**Appropriate** The EAG is satisfied that the search strategies were well reported and appropriate.
Search filters	Appendix D, Section D1.1, pp.33-49	**Appropriate** Search filters were not accurately translated in all cases and some thesaurus headings were exploded in the company search strategy. However, the EAG considers this is unlikely to have led to missing studies.
Eligibility criteria	Appendix D, Section D1.1, Table 70, pp 50-52	**Some concerns** The company included the PD-L1 ≥50%, squamous population sub-group, despite IO monotherapy being the standard of care for these patients according to the NICE clinical pathways for NSCLC. Only studies published in English were included in the SLR, thereby excluding studies published in other languages. The company only included phase 2/3 trials in the systematic literature review and meta-analysis. See Section 3.1.2 for further details.

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Screening	Appendix D, Section D 1.1, Table 70, p. 50-52	**Some concerns** The company did not indicate that they attempted to contact the authors of studies lacking enough information for data extraction and inclusion in the NMA. See section 3.1.3 for details.
Data extraction	Appendix D, Section D 1.1, p. 52	**Appropriate** Data extraction was conducted by two independent reviewers. Any discrepancies that arose were resolved through discussion, with a third reviewer involved if necessary. This independent approach to data extraction significantly reduces the likelihood of errors, enhancing the reliability of the findings.[7]
Quality appraisal	Appendix D, Section D 1.1, Table 77, p. 86	**Appropriate** The company provided the RoB assessment for the nine trials included in the feasibility evaluation for the NMA. All trials were determined to have a low risk of bias according to the Cochrane Collaboration's tool, except for performance bias. Six of the trials were rated as having a high risk of performance bias due to lack of blinding. Following a thorough review, the EAG found the RoB assessment to be appropriate.

Source: Appendix D, Section D1.1, pp.33-68.[8]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; NMA = Network Meta-Analysis; PfC = points for clarification; PD-L1 = Programmed Death-Ligand 1; IO = Immuno-Oncology; RoB = Risk of Bias; IL – First line

3.1.1 Search methods for the clinical effectiveness SLR

The company conducted separate searches for clinical effectiveness studies.[8] The EAG used the PRESS checklist to appraise the search strategies.[9]

3.1.2 Eligibility criteria

3.1.2.1 Population

- As explained in section 2.1, IO + chemotherapy is suitable for the PD-L1 ≥50%, squamous population sub-group when urgent clinical intervention is needed (i.e., when the disease

is progressing quickly). Hence, the EAG is satisfied that the inclusion of patients with PD-L1 ≥50%, squamous histology in the eligibility criteria for the SLR, was appropriate.

- The company included patients with and without brain metastases in the inclusion criteria for the systematic literature review and NMA, which is a good way to cover diverse cases. However, it would have been helpful if the company had stated whether patients with stable brain metastases (e.g. after treatment) or untreated brain metastases were eligible for inclusion. This could influence the results of the NMA significantly as untreated brain metastases are generally more challenging to manage.
- Patients with "newly diagnosed advanced" and "progressed from lower stage to advanced stage" disease are included in the eligibility criteria for the systematic literature review. It would be useful to know the time since progression, but this information was not reported in the CS. Patients who have recently progressed from a lower stage may have different treatment responses compared to those who have been in an advanced stage for longer periods.

3.1.2.2 Language

Eligible studies in the company's SLR were those published in English (CS Appendix D, Table 70, p.50 to p.52).[10] As it has been suggested that studies conducted in non-English speaking countries are more likely to be published in English journals if they have statistically significant results than studies with statistically non-significant results,[11] it is possible that potentially eligible studies may have been excluded from the SLR, particularly for studies involving IOs other than cemiplimab, which the company may not be aware of.

3.1.2.3 Study designs

In CS appendix D, table 70, the company stated that phase I and IV trials, observational studies were excluded.[10] Since focusing on phase 2/3 trials may enhance comparability across trials of different drugs, the exclusion of other study types (e.g., phase I and IV trials; observational studies) was deemed appropriate, although it may restrict the evidence base and potentially overlook valuable safety and efficacy data, particularly in the case of pembrolizumab for which there are likely to be more studies. Although case reports and case series are often considered lower-quality evidence, they can highlight unique cases or rare side effects that may not be captured in larger studies.

3.1.3 Screening

The company states: "Following the screening, 93 studies were included; of these 43 were ongoing without published results and were subsequently excluded" (CS Appendix D.1, p.52).[10] The company did not report whether they attempted to contact the authors of studies lacking enough information, which might have facilitated the inclusion of pertinent data in the SLR/NMA and potentially affected the results.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

A summary of the EAG's critique of the design, conduct and analysis of the EMPOWER-lung 3 trial is presented in Table 3.2.

Table 3.2: Summary of EAG's critique on the design, conduct and analysis of the EMPOWER-Lung 3 trial

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Intervention	B.2.3.1, Table 5, p.36	**Appropriate** Participants received 350mg (IV) of cemiplimab Q3W with four cycles of chemotherapy. Investigators could choose from one of the following chemotherapy options: • Paclitaxel 200mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on Day 1 of every 21 days for 4 cycles • Paclitaxel 200mg/m2 IV plus cisplatin 75mg/m^2 IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500 mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500mg/m2 IV plus cisplatin 75 mg/m2 IV on day 1 of every 21 days for 4 cycles. The EAG is satisfied that the cemiplimab + chemotherapy intervention in the trial is line with the NICE decision problem.
Comparator	B.2.3.1, Table 5, p.36	**Some concerns** Participants received placebo with four cycles of chemotherapy. Investigators could choose from one of the following chemotherapy options: • Paclitaxel 200mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on Day 1 of every 21 days for 4 cycles • Paclitaxel 200mg/m2 IV plus cisplatin 75mg/m^2 IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500 mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500mg/m2 IV plus cisplatin 75 mg/m2 IV on day 1 of every 21 days for 4 cycles. The EAG has some concerns that the flexibility of investigators choice chemotherapy regimens used in the trial is not reflective of chemotherapy regimens routinely used in UK clinical practice.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		See section 3.2.1 for further details.
Randomisation	B.2.3.1, p.34 Appendix D1.3, Table 86, p.91	**Appropriate** Randomisation was performed 2:1 in favour of cemiplimab with chemotherapy versus placebo with chemotherapy via an interactive web response system. The randomisation was stratified by histology (squamous, non-squamous) and PD-L1 expression (<1%, 1-49%, or ≥50%). The EAG is satisfied that the randomisation methods used were appropriate.
Allocation concealment	Appendix D.1.3, Table 86, p.91	**Some concerns** The CS's critical appraisal of allocation concealment for the company's trial was ambiguous. The justification focused on blinding rather than allocation concealment: "Cemiplimab and chemotherapy were prepared for infusion by a pharmacist at the study site. The pharmacist provided site staff with a ready-to-use cemiplimab or placebo infusion solutions that looked identical, allowing the intervention or comparator to be administered in a blinded fashion."
Eligibility criteria	B.2.1, Table 5, p.35	**Appropriate** The inclusion criteria for the trial were: • Patients aged 18 years or older (20 years or older for Japanese participants); • Histologically or cytologically confirmed squamous or non-squamous NSCLC; • ECOG PS ≤1; • Any PD-L1 expression status, • Stage IIIB/C or stage IV NSCLC. • Active or untreated brain metastases were ineligible unless patients were adequately treated, and brain metastases were considered clinically stable • Patients with prior anti-PD-1/PD-L1 therapy and patients whose tumours were positive for EGFR, ALK, or ROS1 mutations were ineligible.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		The EMPOWER-Lung 3 trial enrolled patients with any PD-L1 expression status prior to the MHRA licensing cemiplimab with chemotherapy for use in patients with PD-L1 ≥1%. The company presented efficacy and safety data for patients in the MHRA label population (PD-L1 ≥1%) separately to the results presented for the ITT group (PD-L1 any level). The EAG is satisfied that the eligibility criteria of the trial, for patients in the MHRA label population, reflects the patient population in the NICE decision problem who would be eligible to receive IO + chemotherapy.
Blinding	Appendix D.1.1, Table 86, p.91	**Appropriate** Cemiplimab and chemotherapy were prepared for infusion by an unblinded pharmacist at the study site and provided site staff with a ready-to-use cemiplimab or placebo infusion solutions that looked identical so the treatments were administered in a blinded fashion. A blinded independent review committee assessed de-identified radiographs to determine tumour response. An independent data monitoring committee reviewed safety data that were blinded by treatment arm. The EAG is satisfied that the blinding methods used were considered appropriate to avoid introducing bias into the trial.
Baseline characteristics	B.2.3.2, Table 6, p.40 -41 B.2.7, p.58 Appendix E, Table 91, p.99	**Some concerns** The company report that disease characteristics were well balanced between treatment groups at baseline, including for prognostic factors. However, within the MHRA label population, the EAG notes that there are some differences in baseline characteristics between trial arms including age (% people aged ≥65 years; ~7% difference between groups) and sex (% of females;~5% difference between groups), which could act as treatment modifiers. There is also concern the trial population may not be representative of the UK patient population. See section 3.2.2 for further details.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Dropout rate	Appendix D.1.2, Figure 37, p.90	**Appropriate** The primary reason for treatment discontinuation was disease progression. Of the 312 participants randomised to cemiplimab + chemotherapy group, 240 discontinued treatment, 185 (77%) due to disease progression or death. Of those randomised, the drop-out rate for reasons other than disease progression or death was 23%. Of the 154 randomised to placebo + chemotherapy, 149 discontinued treatment with 110 (74%) due to disease progression or death. Of those randomised, the drop-out rate for other reasons was 26.1%. Other reasons for discontinuation were physician decision, adverse events, withdrawal of consent, patient decision, non-compliance, lost to follow-up and 'other'. The number of drop-outs due to disease progression or death, and other reasons was well balanced between the treatment groups. groups. The EAG does not consider the drop-out rate in the EMPOWER-lung 3 study is likely to introduce bias.
Statistical analyses	B.2.12.1, p.83	**Some concerns** The study was powered to the ITT population (any PD-L1 expression) rather than to the MHRA label population (PD-L1 ≥1%). See section 3.2.3 for further details.
Outcome measures	B.2.3.1, Table 5, p.37	**Appropriate** The primary outcome was overall survival. Other outcomes were progression-free survival, objective response rate, duration of response, best overall response, quality of life and adverse effects. Whilst the company revised to trial protocol to make overall survival rather than progression-free survival the primary outcome, all relevant outcomes in the NICE decision problem were considered by the EAG to be reported adequately.
Results: Efficacy outcomes	B.2.6, pp.49-57	**Appropriate/some concerns** In the MHRA label population (PD-L1 ≥ 1%): • OS was 23.5 months vs 12.1 months in the intervention group vs placebo group (HR = 0.51, 95% CI 0.38-0.69), P<0.0001)

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		• PFS was 8.3 months vs 5.5 months in the intervention group compared to the placebo group (HR = 0.48, 95% CI: 0.37-0.62, P<0.0001) • The ORR was 47.9% (95% CI: 41.1, 54.8) vs 22.7% (95% CI: 15.3, 31.7) in the intervention group versus the placebo group (P < 0.0001). • The duration of response was 17.5 months vs 6.5 months in the intervention group vs the placebo group (HR: 0.40, 95% CI: 0.23, 0.71, P = 0.0013). • Statistically significant differences favouring cemiplimab + chemotherapy versus chemotherapy alone were present for several function and symptom domains on the QLQ-C30 and QLQ-LC13 quality of life tools. For example, pain symptoms at data cut-off compared to baseline were -4.31 (95% CI: -8.07, -0.55) in favour of the intervention (P = 0.0248)'. However, there was a lack of statistically significant difference between comparison groups for most of the quality-of-life outcomes assessed. The EAG agrees with the company's interpretation that PFS, OS, duration of response and specific HRQoL measures demonstrated a clinically meaningful difference favouring cemiplimab with chemotherapy compared to placebo with chemotherapy. However, the results for many HRQoL measures were not statistically significant. See section 3.2.4 for further details.
Results: Adverse events	B.2.10.1, p.73 – p.74	**Appropriate/some concerns** TEAEs was similar between treatment groups with a greater incidence of grade 3 to 5 TEAEs in the cemiplimab + chemotherapy group, twenty-seven (8.7%) receiving cemiplimab + chemotherapy had TEAEs that led to death, compared to 14 (9.2%) in the placebo + chemotherapy group. Ninety-four patients (30.1%) in the cemiplimab group and 37 (24.2%) in the placebo had serious AEs (SAEs). The most common SAEs were pneumonia, anaemia and death in the cemiplimab + chemotherapy group, and febrile neutropenia in the placebo + chemotherapy group.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		Three patients (1.0%) in the cemiplimab + chemotherapy group discontinued and one patient died due to immune related AEs. The company submission reports that discontinuations due to immune-related AEs and AEs were low in the EMPOWER-Lung 3 trial in the context of results previously reported for other IO + chemotherapy regimens. However, [redacted] which is associated with reduced toxicity is important to note. See section 3.2.5 for further details.
Results: Subgroup analyses	Appendix E, p.93 – p.95.	**Some concerns** The company carried out all pre-planned subgroup analysis as specified in the trial protocol. In all MHRA label subgroups (squamous/non-squamous and PD-L1 1-49%/ ≥PD-L1 50%), PFS, OS, and ORR outcomes favoured cemiplimab + chemotherapy compared to placebo + chemotherapy. Whilst there were no statistically significant differences in PFS, ORR, or OS between the subgroups analysed, forest plots indicated that the benefit of conclusion in favour of placebo + chemotherapy was less amongst those aged over 65 years, females, people with an ECOG score of 1, patients with metastatic disease and brain metastasis. See section 3.2.6 for further details.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Source: Company submission document B.[4], Company submission document B appendices.[8] Abbreviations: IV = intravenous; Q3W = every three weeks; AUC = area under curve; EAG = evidence assessment group; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; NSCLC = non-small cell lung cancer; ECOG = eastern cooperative oncology group; ECOG PS = ECOG Performance Status; PD-L1 = Programmed death-ligand 1; EGFR = Epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; ROS = Proto-oncogene tyrosine-protein kinase; ROS 1= ROS proto-oncogene 1; ITT = intention to treat; MHRA = Medicines and Healthcare products Regulatory Agency; IO = immunotherapy; UK = United Kingdom; OS = overall survival; HR = hazard ratio; ORR = overall response rate; CI = confidence interval; GHS = global health status; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = The EORTC Core Quality of Life questionnaire; HRQOL = Health-related quality of life; PFS = progression-free survival; TEAEs = Treatment emergent adverse events; AEs = adverse events; SAEs = severe adverse events; OR = odds ratio		

3.2.1 Comparator

A breakdown of the different chemotherapy regimens used for the ITT trial population was provided by the company (CS section B.2.4, figure 4, p.48); however, a breakdown of the chemotherapy regimens used for the 4 subgroups in the MHRA label population (squamous/non-squamous, PD-L1 1-49%/PD-L1 ≥ 50%) was not provided by the company.[4]

The current chemotherapy regimens used in combination with IO treatments in UK practice are those specified in the Bluteq protocol. For non-squamous histology the chemotherapy options are pemetrexed with platinum chemotherapy, and for squamous histology, the chemotherapy regimens are carboplatin and paclitaxel.[12,13] The clinical expert advised the EAG that in UK clinical practice patients should be fit to receive AUC 6 carboplatin dose. In the cemiplimab + chemotherapy arm of EMPOWER-Lung 3, [redacted] of the participants were selected by investigators at baseline to receive an AUC 6 carboplatin dose, and [redacted] were selected to receive an AUC 5 carboplatin dose. This was to allow more flexibility in the chemotherapy regimen used and reduce the toxic side-effects of AUC 6 carboplatin. Additionally, according to the EAG's clinical advisor, the proportion of non-squamous patients receiving paclitaxel + carboplatin rather than pemetrexed was higher in the company's trial than would be expected in routine NHS care. This may reflect the increased flexibility of chemotherapy regimens in the EMPOWER-Lung 3 trial compared to clinical practice. The EAG is unable to comment on the likely impact of this deviation on trial outcomes.

3.2.2 Baseline characteristics

In the MHRA, label population, the EAG notes that the proportion of patients over 65 years was higher in the cemiplimab + chemotherapy group (40.6%) compared to the placebo + chemotherapy group (32.7%) and the proportion of females in the cemiplimab group (14.7%) was lower than the placebo group (20.0%). However, the EAG's clinical advisor was not concerned that these differences would substantially impact on conclusions.[14]

The EAG has concerns that the baseline characteristics of the trial population may differ from the NSCLC population in the UK. Amongst the MHRA label population in the trial, the median age of participants in the four subgroups was between 59.0 and 63.5 years, and the percentage aged 65 years or older was between 27.3% and 42.6%. The National Cancer Institute estimates the median age for lung cancer diagnosis to be 71 years, and in the UK patient population 45% of lung cancer patients are aged over 75 years.[15,16] This indicates the average age of those in the trial population is likely lower than the average age of the UK NSCLC population. Likewise, in all four subgroups of the MHRA label population, the proportion of male participants was >75% which was considerably higher compared to the 52% proportion of males in the UK patient population.[15]

The clinical advisor noted that brain metastasis was lower than would be expected in the UK population and the imbalance in histology types may be due to the over-representation of males in the trial who are more likely to have squamous disease.

3.2.3 Statistical analyses

The EAG has some concerns that due to the trial being powered to detect significant differences in the ITT population rather than the MHRA population, outcome differences between cemiplimab and placebo treatment groups may not have been adequately reflected. The company reported data showing that many of the HRQoL outcomes were not statistically different, albeit that pain symptoms and time to clinically meaningful deterioration were statistically different for certain measures, favouring the cemiplimab + chemotherapy group. Immunotherapies can cause immune-related adverse events that may impact on patients' HRQoL; a sufficiently powered trial may have greater ability to detect these differences. However, the EAG acknowledges that HRQoL outcomes are harder to quantify than survival outcomes.[17]

3.2.4 Efficacy outcomes

The EMPOWER-Lung 3 study was powered to the ITT population (PD-L1 any level) rather than the MHRA population (PD-L1 ≥1%) and the company noted that '*all analyses of the MHRA label population are therefore exploratory*' (CS section B.2.4.1, p.42).[4] Due to the study being underpowered, the EAG has concerns that differences in many HRQoL outcomes between patients who received cemiplimab + chemotherapy versus chemotherapy alone were not adequately detected. The EAG notes, however, that there was a significant difference in pain symptoms and a delay in time to definitive clinically meaningful deterioration favouring cemiplimab plus chemotherapy for certain functional and specific symptoms. Furthermore, the impacts of treatments on HRQoL outcomes are more difficult to quantify compared to survival outcomes, which may account for the mainly non-significant results for the effects of cemiplimab + chemotherapy compared to chemotherapy alone, on most of the HRQoL outcomes.

3.2.5 Adverse events

The safety outcomes of the EMPOWER-Lung 3 trial were comparable to other studies of immunotherapy + chemotherapy in NSCLC patients. However, these studies involved a less flexible chemotherapy regimen and required participants to receive an AUC 6 carboplatin dose. [redacted] patients in the cemiplimab + chemotherapy arm of EMPOWER-lung 3 study were selected by investigators at baseline to initiate treatment with an AUC 5 carboplatin dose which

is not routinely possible for patients with squamous disease in the UK currently as NHS commissioning policy (Blueteq protocol) mandates that patients are 'fit' to initiate treatment with AUC 6 carboplatin. The EAG's clinical advisor expressed that this should be considered when drawing comparisons between treatment related adverse events between studies as AUC 6 is associated with greater toxicity than AUC 5.

3.2.6 Subgroup Analysis

In the protocol for the EMPOWER-Lung 3 study, sub-group analyses were planned for the following variables: age, gender, race, histology, PD-L1 expression level, ECOG status, geographic region of enrolling site and ethnicity.[1] All of these analyses were undertaken; however, the company noted that: "*EMPOWER-Lung 3 was not powered to evaluate differential effectiveness in subgroups and it should be noted that interpretation of results in some subgroups is limited (e.g. by small patient numbers or by the potential for confounding owing to potential imbalances in prognostic baseline characteristics*." (CS section B.2.7, p.58).[4]

In the EMPOWER-Lung 3 study, females and patients aged over 65 years were under-represented compared to the UK patient population and the clinical expert to the EAG noted that the proportion of patients in the trial with brain metastasis was also lower than would be expected. The forest plots for OS, PFS, and ORR indicate that the treatment benefits of cemiplimab + chemotherapy may be less favourable in females, patients aged over 65, and patients with brain metastasis, but there was no statistically significant difference. The company acknowledges in their submission that the trial was not sufficiently powered for the MHRA label population (PD-L1 ≥1%) which is the population in the NICE scope, and the EAG also notes the relatively small number of females, patients aged over 65 and patients and patients with brain metastasis which preventing robust subgroup analysis. The EAG agrees with the company that the direction of treatment effect was consistent between these sub-populations; however, it does not fully support the company's conclusion that the magnitude of treatment effect was consistent. A trial with adequate numbers of patients in each sub-population would have a higher power to detect differences in treatment effects between subgroups and would be needed to confidently reach these conclusions.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted an NMA to estimate the effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy including studies that investigated these technologies compared to chemotherapy alone. A summary of the EAG's critique of the NMA is provided in **Error! Reference source not found.**.

Table 3.3: Summary of the EAG's critique of the company's indirect comparisons

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	Appendix D1.1, pp. 64-89	**Appropriate** For PFS and OS, the company used a 2-step NMA approach developed by Cope et al.[19] Standard parametric models were fit to all arms of all trials

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
	Regeneron UK Limited. Data on file: Cemiplimab combination NMA report. 2024.[18]	included in the NMA. One parametric model was selected for the base case. The difference in the shape and scale parameters of this parametric model from the shape and scale parameters of the reference treatment (chemotherapy) were estimated using a fixed effect bivariate normal NMA. For adverse events and response, the company used a log-logistic model with a logit link. A fixed effect model was used. See section 3.3.1 for further details.
Included and excluded studies	Appendix D1.1, pp. 53, 55-56	**Appropriate** The exclusion of studies based on lack of NICE recommended treatments and overlapping populations is reasonable. See section 3.3.2 for further details.
Included study characteristics and demographics and transitivity assumption	Regeneron UK Limited. Data on file: Cemiplimab combination NMA report. 2024. p.108	**Key issue 3** The company reported that baseline differences between groups across included trials was not known for the target populations of their NMAs. Therefore, the potential for bias related to this could not be assessed. See section 3.3.3 for further details.
Results	Tables 78-85, Appendix D1.1, pp. 87-89 Appendix Q, pp. 195-206	**Some concerns** The company reported the hazard ratio estimates and presented survival curves with 95% confidence intervals. However, the NMA estimated the shape and scale parameters of the parametric survival curves and the results of these were not presented. See Section 3.3.4 for further details.
Subgroup analyses	Appendix D, pp. 195-206	**Some concerns** The company reported that cemiplimab + chemotherapy was of similar effectiveness to pembrolizumab + chemotherapy for all subgroups. However, the EAG note that this may not be the case for all sub-group analyses. See section 3.3.4 for further details.
Sensitivity analyses	Appendix D1.1, pp 64-89	**Appropriate** The company ran various sensitivity analyses (e.g. broader networks including more active interventions, random-effects models, constant hazard models). Results were very similar in these analyses.

Source: CS Appendix D, Section D1.1, pp.53-89; Appendix Q pp.195-206.[8] Regeneron UK Limited. Data on file: Cemiplimab combination NMA report. 2024.[18]

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
Abbreviations: EAG = Evidence Assessment Group; CS = company submission; PFS = progression-free survival; OS = overall survival; NICE = National Institute for Health and Care Excellence; NMA = Network meta-analysis		

3.3.1 Statistical methods

The EAG agreed the rationale for conducting a NMA was appropriate, given the lack of RCTs comparing the effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy. A summary of the methods used, with the EAG's critique, is provided below.

3.3.1.1 *Two-step NMA*

NMA models for PFS and OS were conducted using a 2-step method, which allows for hazard ratios to vary over time.[19] The EAG agrees this is an appropriate method for analysing these data, since the proportional hazard assumption was likely violated for some outcomes (e.g. OS).

The first step involves fitting a standard set of parametric survival models to reconstructed individual participant data for OS and PFS for each trial arm (exponential, Gompertz, Weibull, log-normal, log-logistic, gamma and generalized gamma). The best-fitting parametric distributions were selected based on goodness of fit (AIC), plausibility of underlying assumptions, and plausibility of model fit within-trials.

The second step then uses the scale (how spread out the distribution) and shape (the shape of the distribution) parameters from the first step to estimate time-varying hazard ratios for all interventions included in the Bayesian multivariate NMA model.

3.3.1.2 *Heterogeneity and Fixed effect models*

Fixed effect models were used for all analyses as there were very few trials included in analyses. For example, base-case analyses that included all participants with PD-L1≥1% were based on four trials. The EAG agreed that there was an insufficient number of trials to model between-study heterogeneity therefore it was appropriate to use fixed effect models. However, the disadvantage is that there is no way to quantify heterogeneity, a key factor for evaluating the validity of these analyses.

3.3.2 Included and excluded studies

Thirty-seven trials were excluded due to no recommended NICE intervention. Three trials were excluded due to overlapping populations with their respective global trials, 10 studies were included (see table 3.4, below). While the exclusion of studies may lead to the exclusion of indirect evidence, given the lack of direct comparisons between active interventions, the impact on effect estimates for key comparators is likely to be minimal. Evidence networks for the base case analyses (PD-L1 ≥1%, any histology) are presented in Figure 3.1 and Figure 3.2.

Table 3.4 Trials available for each histology population

Trial	Scenario	Intervention/Comparator
R2810-ONC-16113 (pt.2)[1]		Cemiplimab + IC chemotherapy vs. IC chemotherapy (cisplatin/carboplatin + paclitaxel/pemetrexed)
KEYNOTE-024[20]		Pembrolizumab vs. IC chemotherapy (carboplatin/cisplatin + pemetrexed/gemcitabine or carboplatin + paclitaxel)
KEYNOTE-042[21]		Pembrolizumab vs. IC chemotherapy (carboplatin + paclitaxel/pemetrexed)
KEYNOTE-021G[22]		Pembrolizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed
KEYNOTE-189[23]		Pembrolizumab + IC chemotherapy vs. IC chemotherapy (cisplatin/carboplatin + pemetrexed)
KEYNOTE-407[24]		Pembrolizumab + IC chemotherapy vs. IC chemotherapy (carboplatin + paclitaxel/nab-paclitaxel)
IMpower110[25]		Atezolizumab vs. IC chemo (carboplatin/cisplatin + pemetrexed/gemcitabine)
IMpower130[26]		Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel
IMpower150[27]		Atezolizumab + carboplatin + paclitaxel[a] vs. atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel[b]
PAULIEN[28]		Pembrolizumab vs. pembrolizumab + platinum chemotherapy (regimens not specified)

Reproduced from Table 4-1, page 57 in the company NMA report.[18]
Notes: *For a given trial, IC chemotherapy regimens in the immunotherapy combination arm are identical to those listed in the comparator arm. Scenario colors correspond to the following: PD-L1 ≥1%, any histology; PD-L1 1-49%, squamous histology; PD-L1 ≥50%, squamous histology; PD-L1 1-49%, non-squamous histology; PD-L1 ≥50%, non-squamous histology; PD-L1 ≥1%, squamous histology; PD-L1 ≥1%, non-squamous histology; PD-L1 1-49%, any histology; PD-L1 ≥50%, any histology; any PD-L1, any histology.* ***a)*** *Atezolizumab + carboplatin + paclitaxel is not recommended by NICE but was included to facilitate the indirect comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel;* ***b)*** *Bevacizumab + carboplatin + paclitaxel was not considered to be a relevant comparator and was therefore excluded from the feasibility assessment.*
Abbreviations: *IC, investigator's choice; NICE, National Institute for Health and Care Excellence.*

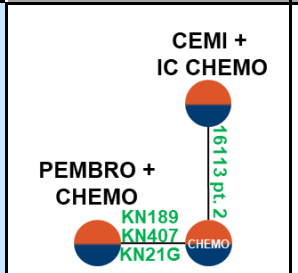
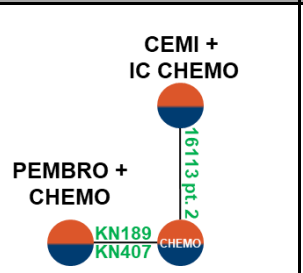
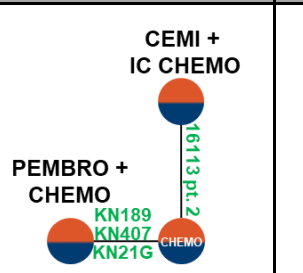
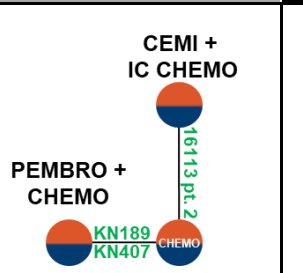
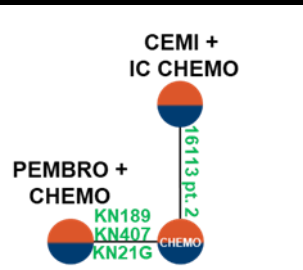
Scenario	Overall survival		Progression-free survival		ORR
	Constant HR	Time-varying HR	Constant HR	Time-varying HR	
PD-L1 ≥1%, any histology (efficacy base case)					

Figure 3.1 Reproduced from Figure 4-4, p.79 in the company NMA report:[8] evidence network diagrams for overall survival, progression-free survival and response

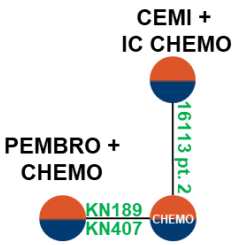
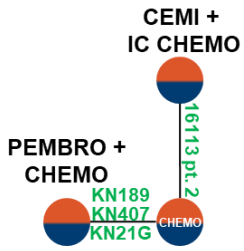
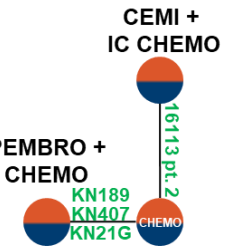
Scenario	Safety		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAEs
Any PD-L1, any histology (safety base case)			

Figure 3.2 Reproduced from Figure 4-4, p.88 in the company NMA report:[8] evidence network diagrams for safety

3.3.3 Transitivity assumption

The company acknowledge it is not possible to assess the validity of the transitivity assumption for all their NMA models. First, almost all analyses had no closed loops – which are necessary for comparison of direct and indirect evidence.

An additional difficulty is that all trials included a combination of patients with PD-L1 <1% and PD-L1 ≥1%. Since baseline characteristics were not reported according to PD-L1 status for any comparator trials, the company noted it was not possible to formally assess the transitivity assumption as the necessary baseline characteristics for key effect modifiers, in the target population, were not available.

However, it was possible to identify differences between trials for some potential prognostic factors:

- Chemotherapy regimens differed across trials (for example, trials differed in terms of provision of paclitaxel, nab paclitaxel, pemetrexed, carboplatin, cisplatin and their combinations); this variation may have impacted on effect estimates.

- Trials of pembrolizumab and chemotherapy allowed for treatment switching (but did not report data adjusted for effects of crossover). In contrast, the company's EMPOWER Lung-3 trial did not allow for treatment switching. This difference in study design may favour cemiplimab as treatment switching could dilute the treatment effect for pembrolizumab and chemotherapy. The company reported that the % of patients in the chemotherapy arms of the comparator trials who received subsequent pembrolizumab treatment was not reported at the relevant timepoints. However, 41-42% had received pembrolizumab in study crossover at 5 years in the KEYNOTE-189 and KEYNOTE-407 studies.

3.3.4 Results

3.3.4.1 *PFS and OS*

Hazard ratios at different time points for the log-logistic model are reproduced from the CS below (see Tables 3.5 and 3.6). The company produced results for the other parametric models which were similar, and consequently only reported the log-logistic results. The log-logistic model was the best fitting model according to the total AIC and BIC across the trial arms of the studies included in the NMA.

The company claimed that these analyses suggested comparable efficacy between pembrolizumab + chemotherapy and cemiplimab + chemotherapy. The EAG partially agree with these conclusions. Differences in the NMA were not statistically significant and effect estimates generally favoured cemiplimab + chemotherapy. Therefore, it is plausible that this treatment is at least as effective as pembrolizumab + chemotherapy. However, the EAG also note the 95% credible intervals were too wide to rule out important differences either in favour of pembrolizumab + chemotherapy or cemiplimab + chemotherapy. In agreement with the company, the transitivity issues mentioned in Section 3.3.3 should be considered in the interpretation of the results.

Table 3.5 OS NMA results for the PD-L1 ≥1%, any histology scenario (log-logistic, fixed effect model)

Cemiplimab + chemotherapy versus	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	0.94 (0.52, 1.57)	0.90 (0.60, 1.32)	0.88 (0.62, 1.26)	0.87 (0.62, 1.26)	0.87 (0.61, 1.28)	0.87 (0.60, 1.30)	0.88 (0.60, 1.31)	0.88 (0.60, 1.32)

Reproduced from Table 4-3, page 90 in the company NMA report.[18]
Notes: *Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. The model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.*
Abbreviations: *CrI, credible interval; HR, hazard ratio.*

Table 3.6 PFS NMA results for the PD-L1 ≥1%, any histology scenario (log-logistic, fixed effect model)

Cemiplimab + chemotherapy versus	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	1.09 (0.77, 1.53)	1.06 (0.79, 1.45)	1.04 (0.76, 1.45)	1.03 (0.74, 1.45)	1.02 (0.72, 1.43)	1.01 (0.72, 1.42)	1.00 (0.72, 1.40)[a]	1.00 (0.72, 1.38)[b]

Reproduced from Table 4-4, page 92 in the company NMA report.[18]
Notes: *Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. Model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.*
a) HR 1.0044 (95% CrI 0.7202, 1.3957); b) HR 1.0010, 95% CrI 0.7229, 1.3804
Abbreviations: *CrI, credible interval; HR, hazard ratio*

3.3.4.2 *Subgroup* analyses for OS and PFS

Results from the subgroup analyses (PD-L1 status, and squamous vs non-squamous) were largely similar to the base-case NMA analyses (PD-L1 ≥1%) of OS and PFS. As expected, given the smaller sample size found in subgroup analyses, the 95% CrIs were wider than in the base-case.

However, for the PD-L1 1-49% squamous group, PFS favoured pembrolizumab + chemotherapy over cemiplimab + chemotherapy (HR 1.49, 95% CrI 0.80 to 2.76, 24 month follow up), although the 95% CrI overlaps with no difference. This effect estimate is more favourable to pembrolizumab + chemotherapy than found for the base-case (PD-L1 ≥1%) PFS (HR 1.01, 95% CrI 0.72 to 1.42); however, there is overlap in 95% CrIs between the base-case (PD-L1 ≥1%) and PD-L1 1-49% squamous group. In contrast, for the PD-L1 1-49% squamous group, OS favoured cemiplimab + chemotherapy (HR 0.84, 95% CrI 0.44 to 1.60, 24 month follow up) in a similar way to the base-case.

3.3.4.3 *Adverse effects*

Cemiplimab + chemotherapy was associated with increased odds for Grade 3 to 5 all-cause adverse events, although the 95% credible interval included 1 (i.e. no difference). For Grade

3 to 5 IMAEs and discontinuation due to all-cause adverse events, 95% credible intervals were too wide to draw any conclusions. For further details, see Table 3.7, which reproduces Table 17 from the CS.

Table 3.7: Safety NMA results for the any PD-L1, any histology scenario (fixed effect)

Cemiplimab + chemotherapy versus	OR (95% CrI)		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAE
Pembrolizumab + chemotherapy	1.53 (0.95, 2.49)	1.58 (0.27, 9.78)	0.55 (0.22, 1.50)

Reproduced from Table 17, CS document B, p.70.[4]

Notes: *AE, adverse event; CrI, credible interval; DAE, discontinuation due to all-cause AEs; IMAE, immune-mediated AE; NMA, network meta-analysis; OR, odds ratio*

3.4 Conclusions of the clinical effectiveness section

The EAG had concerns regarding differences between the NICE scope and the company's decision problem in relation to the comparators and population of interest. Specifically, the company only included one comparator (pembrolizumab + chemotherapy) despite multiple treatments being included in the NICE scope. Also, the company included the PD-L1, squamous population despite the standard of care for this population sub-group being IO monotherapy. After querying both issues with the company in the PfCs and with the clinical advisor to the EAG, the EAG concludes that pembrolizumab + chemotherapy is the relevant comparator and that the PD-L1 ≥50%, squamous population sub-group is relevant in certain situations, e.g. IO + chemotherapy would be the standard of care first line treatment for this population sub-group when urgent clinical intervention is needed, including where the disease is progressing rapidly. However, the EAG has raised these as key issues, to make the NICE committee aware that cemiplimab + chemotherapy is only appropriate for administration to patients who would otherwise have received pembrolizumab + chemotherapy.

In relation to the SLR, several concerns were raised, including the exclusion of non-English studies and of phase I/ IV trials and observational studies. None of these points were identified by the EAG as being key issues; however, they are important to note.

The EAG believe the EMPOWER-Lung 3 trial was mainly conducted appropriately; however, several issues were identified. The first issue to note is that the flexibility of investigators' choice chemotherapy regimens used in the trial is not reflective of chemotherapy regimens routinely used in UK clinical practice. It is feasible that this flexibility will be allowed in clinical practice should NICE recommend the use of cemiplimab + chemotherapy; however, this issue does reduce comparability with the pembrolizumab + chemotherapy, for which there is less flexibility regarding the accompanying chemotherapy regimens. The EAG also has concerns that the trial population may not be representative of the UK patient population, with the trial sample having a younger age profile and a much smaller proportion of females compared to UK clinical practice. The EAG also has concerns in relation to the fact that the EMPOWER-Lung 3 trial was powered to the ITT population (any PD-L1 expression) and was underpowered for the MHRA label population (PD-L1 ≥1%) which is the population in the NICE scope, and how this may have impacted the detection of significant effects, particularly in sub-

group analyses and in relation to HRQOL outcomes. None of these points were identified by the EAG as being key issues; however, they are important to note.

The results from the NMA indicated comparable effectiveness between cemiplimab + chemotherapy compared to pembrolizumab + chemotherapy overall, although with very wide credible intervals. The EAG noted greater uncertainty around the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group for PFS as the estimate favoured pembrolizumab + chemotherapy in this population, again with very wide credible intervals. The transitivity assumption could not be assessed using statistical methods as there were no closed loops within the NMA network to enable comparisons between direct and indirect evidence for the effectiveness of cemiplimab + chemotherapy versus pembrolizumab versus chemotherapy. Furthermore, there was a lack of information regarding the degree of homogeneity in relation to the PD-L1 status of patients within each trial. Additionally, patients in the pembrolizumab + chemotherapy trials were allowed to switch between treatment after disease progression, which was not the case in the EMPOWER trial of cemiplimab, resulting in an unknown percentage of patients receiving immunotherapy in the control arms of the pembrolizumab trials by the data cut timepoint for the NMA analyses in the CS. This may affect the OS hazard ratio time-varying estimates. Variations in the chemotherapy regimens received by patients in each trial were also apparent. These issues introduce uncertainty into the NMA results as they undermine the comparability of trials within the network. The EAG has identified this as a key issue.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

This section pertains mainly to the review of cost-effectiveness analysis studies. However, the search section also contains summaries and critiques of other searches related to cost-effectiveness presented in the company submission. Therefore, the following section includes searches for the cost-effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

Table 4.1 presents an overview of the EAG's critique of the methods used to identify studies for the review of cost-effectiveness.

Table 4.1: Summary of the EAG's critique of the methods for the review of cost-effectiveness

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Data sources for cost-effectiveness analysis review	Appendix G, Appendix H, Appendix I	**Appropriate** Two parallel systematic reviews were carried out by the company in January 2020, with updates in January 2021, May 2022, and May 2024. The May 2024 update had a UK specific focus while the earlier reviews were conducted with a global scope. Given the rapidly evolving treatment landscape, a date restriction of the year 2009 was applied to the main database searches. The first systematic review focussed on published cost-effectiveness/cost-utility analyses and health resource utilisation, whilst the second systematic review focussed on HRQoL studies. An appropriate range of electronic bibliographic databases and HTA websites were searched. These main database searches were augmented with a search of specific conference proceedings, grey literature and supplementary hand-searching. Relevant citations identified through the conference proceedings were also checked for additional relevant studies. The second systematic review focussed on Health-related quality-of-life studies. The review methods were almost identical to the systematic review on cost-effectiveness/cost-utility analyses and health resource utilisation, with the exception that HTA body hand-searches were not performed as relevant data was assumed to be captured via the inclusion of HSUV data in the HTA body hand searches performed as part of the economic SLR.
Search strategies	Appendix H, 1.1, p. 128-148	**Appropriate** The search strategies used to find cost-effectiveness studies were fit for purpose.

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Search filters	Appendix H, 1.1, p 128-148	**Some concerns** The EAG is concerned that the HRQoL study type filter has been altered, potentially making the filter less sensitive. Please see Section 4.1.1 for further comment.
Data sources for model input	Appendix G, Appendix H, Appendix I	**Appropriate** Nineteen economic evaluation studies with UK relevant data were identified as part of the SLR and subsequent updates, including nine previous NICE technology appraisals. Seven alternative HSUV sources were identified in the SLR.
Eligibility criteria for inclusion of economic evaluations	Appendix G, 1.1, Table 95	**Appropriate** The eligibility criteria were appropriate to capture cost-effectiveness studies in this area.
Eligibility criteria for inclusion of health state utility value studies	Appendix H, 1.1, Table 98	**Appropriate** The eligibility criteria were appropriate to capture quality of life in this area.
Eligibility criteria for inclusion of resource use and cost studies	Appendix G, 1.1, Table 95	**Appropriate** The eligibility criteria were appropriate to capture resource use and costs in this area.

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HTA = health technology assessment; HSUV = health-state utility values; SLR = systematic literature review; NICE = National Institute for Health and Care Excellence

4.1.1 Search filters

The company conducted separate searches for clinical effectiveness studies.[8] The EAG used the PRESS checklist to appraise the search strategies.[9]. The HRQoL study type filter used by the company came from the Canadian Agency for Drugs and Technologies in Health (CADTH).[10,29] On closer inspection, the EAG identified that the original HRQoL study type filter had been modified, excluding MeSH terms, keywords and using different search fields. The company did not provide a rationale for the alteration from the original filter or report this alteration in the search methods. This would make the filter less sensitive and impact locating relevant studies. However, no terms were missing from both MeSH and keywords and so the overall impact on the retrieved studies is likely to be relatively small.

4.1.2 Conclusions of the cost effectiveness review

The SLR conducted by the company found a total of 19 economic evaluation studies containing UK relevant data, including nine previous NICE technology appraisals. The data identified in the SLR informed the overall model structure used by the company and several other inputs for the CEM. Although the EAG has some concerns regarding the HRQoL study

type filter used by the company, overall is satisfied that the cost effectiveness review has been conducted appropriately.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2 summarises the NICE reference case checklist and the EAG's assessment on the company's submission in relation to their base-case analysis.

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	Cemiplimab with chemotherapy for adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations.	**Key Issue 1** The population who would be eligible to receive cemiplimab + chemotherapy is a subset of the NICE scope. The EAG consider this to be a key issue in the CS. See section 2.1 for further details.
Comparators	For people with squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Platinum doublet chemotherapy • Pembrolizumab with carboplatin and paclitaxel For people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Platinum doublet chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy	**Key issue 2** The company only included one comparator (pembrolizumab + chemotherapy) in their decision problem, despite various other treatment options being available in the NICE scope and clinical pathways for the population of interest. The EAG consider this to be a key issue in the CS. See section 2.2 for further details.

Element of health technology assessment	Reference case	EAG comment on company's submission
	• Pembrolizumab with carboplatin and paclitaxel (for people in need of urgent clinical intervention) For people with non-squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Atezolizumab with bevacizumab, carboplatin and paclitaxel • Pemetrexed with platinum doublet chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pemetrexed with platinum doublet chemotherapy	
Perspective on outcomes	• Progression-free survival • Response rates • Overall survival • Adverse effects of treatment	**Appropriate** The EAG considers the perspective on outcomes to be appropriate.

Element of health technology assessment	Reference case	EAG comment on company's submission
	• Health-related quality of life	
Perspective on costs	NHS and personal social services (PSS)	**Appropriate** The EAG considers the perspective on costs was adequately captured.
Type of economic evaluation	Cost-utility analysis with a fully incremental analysis	**Some concerns** The company presented a CUA with a fully incremental analysis; however, they also presented a cost-comparison analysis (assuming equivalent clinical outcomes) as an alternative base case.
Time horizon	Long enough to reflect all important differences in costs and outcomes between the technologies being compared	**Appropriate** A 30-year time horizon was used for the cost-effectiveness analysis. This was considered to be appropriate given the baseline median age of the target population.
Synthesis of evidence on health effects	Based on a systematic review	**Key issue 3** In the absence of head-to-head trials of cemiplimab + chemotherapy vs relevant comparators, an NMA was conducted. The EAG identified several issues with this NMA, including the uncertainty of the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group, the fact that the transitivity assumption could not be assessed, the lack of information regarding the degree of homogeneity in relation to the PD-L1 status of patients within each trial, the difference in the extent of treatment switching between trials and the variations in the chemotherapy regimens received by patients in each trial. The EAG consider this to be a key issue in the CS. See section 3.3.3 for further details.

Element of health technology assessment	Reference case	EAG comment on company's submission
Measuring and valuing health effects	Quality of life to be presented in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Some concerns** Data on quality of life was gathered from EORTC-QLQ C30 collected in EMPOWER-Lung 3 mapped to the EQ-5D-3L. The use of mapping algorithms introduces additional uncertainty into the estimates of quality of life for the different health states included in the model. See Section 4.2.6 for further details.
Source of data for measurement of health-related quality of life	Reported directly by the patients or carers or both.	**Appropriate** Reported directly by patients in the EMPOWER-Lung 3 trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	**Appropriate** EQ-5D values were scored in accordance with current NICE guidelines.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	**Appropriate** No decision modifiers were applied on the results.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	**Appropriate** Costs and resource use sourced from NHS reference costs, PSS,[30] BNF,[31] eMIT[32] and previous NICE technology appraisals in this clinical area consistent with the NICE perspective. Due to the lack of information in the EMPOWER-Lung 3 trial,[1] information regarding the duration of subsequent treatments were based on estimates reported in Insinga et al. (2021).[33] The EAG consider this source to be appropriate.
Discounting	The same annual rate for both costs and health effects (3.5%)	**Appropriate** Discounting of costs and outcomes was in line with NICE guidelines.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source: CS Section B.3.6, Table 62 Abbreviation: EAG = Evidence Assessment Group; CS = company submission; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PSS = Personal Social Services; QALY = quality adjusted life-year; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand-1; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; ROS-1 = ROS proto-oncogene 1; CUA = cost utility analysis; BNF = British National Formulary; eMIT = Drugs and pharmaceutical electronic market information tool; QLQ C30 = The EORTC Core Quality of Life questionnaire		

4.2.2 Model design and assumptions

The company cost-effectiveness model (CEM) is reproduced in Figure 4.1. The company CEM was based on a 'time-in-state' strucuture (otherwise known as a 'partitioned survival model' (PSM) or 'area under the curve (AUC) model'). This is a common model used in NSCLC, and is the approach used in the majority of the prior NSCLC NICE appraisals. Patients begin in the pre-progression health state, where they receive either cemiplimab or a relevant comparator treatment and are progression-free. Patients then transition to the death state over time, or to the post-progression health state, where they receive subsequent treatment. Patients who transition to the post-progression state then move to the death state over time. The proprtion of patients in the pre-progression health state reduces over time according to hazard rates at which patients leave this state, which corresponds to PFS. The proportion of patients who died increases over time according to death rates corresponding to OS. The difference between the proportion of patients alive and the proportion of patients in the pre-progression health state represents the proportion of patients in the post-progression health state.

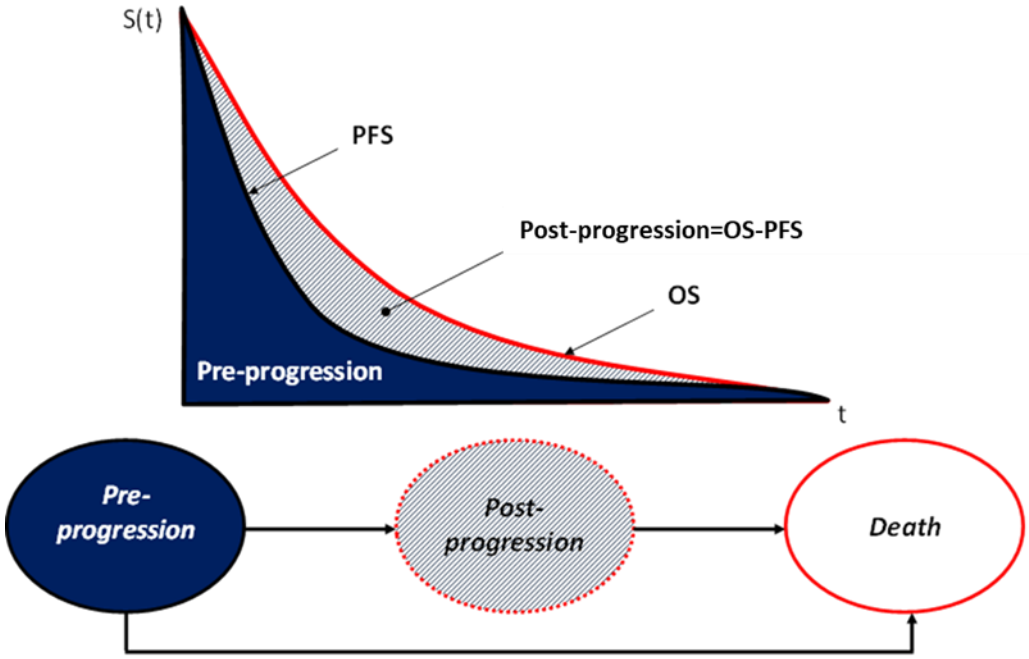


Figure 4.1: Model structure
Source: CS Document B, section B.3.2.1, Figure 14
Abbreviations: CS = company submission

Error! Reference source not found. Table 4.3 summarises the EAG's critique on the model structure adopted by the company.

Table 4.3: Summary of EAG's critique on the design of the economic model

Analysis feature	Section in CS where methods are reported	EAG's assessment
Type of model	Section B. 3.2.1, p.95	**Appropriate** A PSM was used, a structure which aligns with the vast majority of prior NSCLC NICE appraisals. There are several well-known potential issues with the use of PSMs (principally that PFS and OS are modelled independently despite being inherently linked); however, the company have clearly noted these limitations in their submission. The EAG considers the model structure to be appropriate.
Treatment effectiveness	Section B.2.9, p.61	**Key Issue 3** In the absence of a head-to-head RCT, the company used the evidence from the NMA to derive estimates of relative treatment effects between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

Analysis feature	Section in CS where methods are reported	EAG's assessment
		Specifically, the relative treatment effects from the NMA are "anchored" onto the estimates of PFS/OS in the reference arm. As discussed in Section 3.3, the EAG considers the uncertainty surrounding the NMA to be a key issue in the CS; however, the EAG considers the methods used to integrate the results from the NMA into the CEM to be appropriate.
Time-to-event analysis and extrapolation methods	B.3.3.1, p.102	**Appropriate** A standard set of parametric survival models were fit to the OS/PFS data for the chemotherapy reference arm to extrapolate treatment effects for cemiplimab + chemotherapy and pembrolizumab + chemotherapy. To select the most appropriate model, the company used both technical and clinical validation, including the total AIC across all trial arms included in the NMA. See section 4.2.3 for further details. The EAG is satisfied that the time-to-event analysis itself has been conducted appropriately, however has some concerns related to the baseline characteristics of the NMA trials which form part of the validation for model selection. See section 3.3.3 for further details.
Treatment discontinuation	Section B.3.5.1, p.161	**Key Issue 4** In the base case CEM, the company assumes that TTD is equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, implying that all patients remain on treatment until they progress. The EAG has some concerns regarding these estimates for TTD. See section 4.2.4 for further details.
Treatment waning assumption	Section B.3.3.3, p.131	**Key issue 5** In the company base case, the treatment effect was assumed to last five years (three years beyond the two-year stopping rule), with the hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy assumed to be equal to chemotherapy (HR=1) at the end of the fifth year. The EAG consider this 'immediate waning' of the treatment effect to be a strong assumption. The EAG regard the treatment waning assumption as a key issue in the CS. See section 4.2.5Treatment waning assumption for further details.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Model predictions		**Appropriate** The company validated their model assumptions with an advisory board and externally validated their model predictions on appropriate data. The EAG is satisfied with this approach. See Section 4.2.3 and Section 5.4.2 for further details.

Source: EAG output
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; PSM = Partitioned Survival Model ; NSCLC = non-small cell lung cancer; PFS = progression free survival; OS = overall survival; RCT = randomised controlled trial; NMA = network meta-analysis; CEM = cost-effectiveness model; TTD = time to death; HR = hazard ratio

4.2.3 Time to event analysis and extrapolation methods

The PFS and OS survival curves were estimated using a 2-step NMA (see section 3.3). The first part involved fitting a standard set of parametric survival models to the OS/PFS data for each trial arm in the studies included in the NMA: exponential, Gompertz, Weibull, log-normal, log-logistic, gamma and generalized gamma. More flexible models were not considered. The second part involved conducting an NMA with the transformed shape and scale parameter estimates and standard errors.

To select the most appropriate model for use in the economic model, the company used both technical and clinical validation, including:

- Statistical goodness of fit based on Akaike's information criterion (AIC) and Bayesian information criterion (BIC)
- Visual goodness of fit
- Compatibility of parametric model fit to reference curve and NMA model
- Base-case NMA model
- External validation of OS data
- Validation of extrapolations by UK clinical expert lung oncologists
- Relationship between PFS and OS
- General mortality

For PFS, the company chose the log-logistic model in the base-case, on the basis that the model had the best fit to the chemotherapy hazards, best statistical goodness of fit to chemotherapy, was the favoured NMA model and had plausible survival projections. Figure 4.2 shows the various parametric fits for PFS for the chemotherapy arm from the EMPOWER-Lung 3 trial, and Table 4.4 shows the validation summary for the PFS model selection.

Figure 4.2 EMPOWER-Lung 3 chemotherapy PFS parametric fits

Table 4.4 Validation summary table for PFS model selection

Model	NMA Model	Goodness of Fit			Two-year PFS estimates			Decision
		AIC	BIC	Total AIC across NMA	Chemo (reference)	Cemi+ chemo	Pembro + chemo	
Exponential	Deprioritized	569.23	571.93	6,649.02	4.1%	22.8%	24.5%	Deprioritized
Weibull	Deprioritized	566.12	571.52	6,629.87	2.1%	21.9%	17.8%	Deprioritized
Gompertz	Deprioritized	571.23	576.63	6,546.04	4.1%	24.3%	19.8%	Deprioritized
Log-normal	**Favoured** (second lowest total AIC)	**559.03**	**564.44**	6,519,42	5.0%	23.1%	**25.0%**	Scenario
Log-logistic	**Favoured** (lowest total AIC)	**552.73**	**558.13**	**6,488.58**	**4.8%**	21.5%	23.1%	**Base Case**
Gamma	Deprioritized	562.51	567.91	6,638.30	2.0%	21.3%	24.7%	Deprioritized
Generalised gamma (fixed Q)	**Favoured** (third lowest total AIC)	559.25	564.65	6,520.00	5.1%	**23.2%**	**25.0%**	Deprioritized

Source: CS Table 34, p.119
Abbreviations: PFS = progression-free survival; AIC = Akaike information criterion; BIC = Bayesian information criterion; NMA = network meta-analysis

Table 4.5 Validation summary table for OS model selection

Model	NMA Model	Goodness of Fit			Five-year OS estimates			Decision
		AIC	BIC	Total AIC across NMA	Chemo (reference)	Cemi+ chemo	Pembro + chemo	
Exponential	Excluded due to PH violations'	602.89	605.59	6,995.24	3.7%	17.2%	11.9%	Excluded
Weibull	Deprioritized	602.61	608.01	6,951.62'	1.8%	11.9%	6.5%	Deprioritized
Gompertz	Favoured (second lowest AIC)	603.71	609.11	6,928.61	0.8%	5.7%	3.4%	Deprioritized
Log-normal	Deprioritized	610.18	615.58	6,958.01	9.4%	25.0%	19.8%	Deprioritized
Log-logistic	**Favoured** (lowest total AIC)	604.20	609.60	6,925.18	8.4%	21.5%	17.6%	**Base case**
Gamma	Deprioritized	602.52	607.92	6,957.13	2.2%	13.6%	9.2%	Deprioritized
Generalised gamma (fixed Q)	**Favoured** (third lowest total AIC)	603.44	613.54	6,933.79	5.3%	19.5%	14.6%	Scenario

Source: CS Table 40, p.128-129
Abbreviations: OS = overall survival; AIC = Akaike information criterion; BIC = Bayesian information criterion; NMA = network meta-analysis

As shown in Table 4.4, for PFS the Log-logistic distribution had the lowest AIC and BIC and best fit to the chemotherapy hazards (4.8%) based on the landmark survival at two years from the EMPOWER-Lung 3 trial. It also had the lowest total AIC and BIC across all trial arms included in the NMA. It is worth noting that the Generalized gamma model had both the third lowest AIC and BIC and most accurate estimates of two-year PFS based on the landmark survival at two years for both cemiplimab + chemotherapy (23.2%) and pembrolizumab + chemotherapy (25.0%) from the EMPOWER-Lung 3 trial[1] and KEYNOTE-189[34] and KEYNOTE-407[35] respectively. Whilst the log-logistic distribution is retained by the EAG in the EAG base case, as part of the additional EAG analysis, the EAG have included an additional scenario analysis using the Generalized gamma model for PFS.

For OS, the company chose the log-logistic distribution in the base case, on the basis that it was the favoured NMA model, had “AIC/BIC similarity” and had plausible survival projections. **Error! Reference source not found.** shows the various parametric fits PFS for the chemotherapy arm from the EMPOWER-Lung 3 trial, and **Error! Reference source not found.Error! Reference source not found.** shows the validation summary for the PFS model selection. As shown in **Error! Reference source not found.**, for OS the log-logistic distribution had the 5th lowest AIC and the 5th lowest BIC. The Table 36 of the CS, the company present the total AIC across the OS NMA models and use these figures (in which the AIC across all study treatment arms were summed) to justify the use of the log-logistic distribution in the base case. Despite being having the lowest AIC and second lowest BIC, the Gamma model was “deprioritised” because of the summed AIC. The log-logistic distribution has been retained by the EAG in the base case, however the EAG have included an additional scenario analysis using the gamma model for OS. Overall, the EAG are satisfied that the survival analysis has been conducted appropriately.

Figure 3: EMPOWER-Lung 3 chemotherapy OS parametric fits

4.2.4 Treatment discontinuation

The EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond disease progression under certain conditions, with an estimated HR compared to PFS of 1.17. As shown in Table 4.6, the corresponding HR for pembrolizumab was 0.84, calculated from the KEYNOTE-407 and KEYNOTE-189 trials and weighted by the split of squamous and non-squamous patients in EMPOWER-Lung 3.

Table 4.6: Hazard ratios available to estimate time on treatment in the model

Treatment	Estimated hazard ratio	Source
Cemiplimab + chemotherapy	1.17	EMPOWER-Lung 3
Pembrolizumab + chemotherapy	0.84	KEYNOTE 407 and KEYNOTE 189, split by squamous and non-squamous in EMPOWER-Lung 3
Source: CS Document B, Table 53		

In the base case analysis, the company assume that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, guided by an advisory board meeting where advisors were cautious about concluding discrepancies between the between

cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms, suggesting that *"these differences might be due to IO experience bias or reporting variations between trials"*.

The EAG note that assuming that ToT is equal to PFS ignores the fact that ToT has an impact on PFS and OS, and that for consistency with the effectiveness estimates the ToT estimates should either be estimated from the respective clinical trials (EMPOWER-Lung 3 and KEYNOTE-407) or should assumed to be equal. Assuming that ToT is equal PFS will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy. The company included a scenario analysis where the estimated individual hazard ratios for the different treatment arms shown in Table 4.6 were used, which changed the incremental cost from [redacted] in the base case to [redacted]. The EAG have explored alternative assumptions regarding ToT as part of the EAG analysis/base case.

4.2.5 Treatment waning assumption

As stated in the CS, patients in the EMPOWER-Lung 3 trial[1] and the KEYNOTE-407[35] and KEYNOTE-189[34] trials received cemiplimab and pembrolizumab for a maximum of 24 months. To model the treatment effect beyond this 24-month period, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which the estimated hazard of death is assumed to be equal to chemotherapy at five years for both PFS and OS. The company justified this assumption by stating that UK clinical experts consulted by the company would expect patients to continue to experience treatment benefit following two years of IO treatment, with T-cell activation through three to five years. Furthermore, the company referenced two previous NICE appraisals for pembrolizumab + chemotherapy (TA683[36] and TA770[37]) in which treatment continuation was discussed. In TA683 a linear treatment waning from three to five years was accepted by the NICE committee, and in TA770 the committee accepted a treatment effect lasting to five years based on five-year follow up from KEYNOTE-407.

The company included three sensitivity analyses related to the waning of the treatment effect (Scenario 5, Scenario 6 and Scenario 7):

- Scenario 5 applies a linear treatment waning effect to PFS/OS from 36 months rather 60 months, reducing the incremental QALYs from [redacted] to [redacted] and changing the incremental costs from [redacted] to [redacted]
- Scenario 6 applies a linear treatment waning effect to PFS/OS starting at 36 months and ending at 60 months, reducing the incremental QALYs from [redacted] to [redacted] and changing the incremental costs from [redacted] to [redacted]
- Scenario 7 assumes a continuation of the treatment effect (no treatment waning), increasing the incremental QALYs from [redacted] to [redacted] and changing the incremental costs from [redacted] to [redacted].

The EAG is concerned that the assumption of an 'immediate' waning after five years in the company base case is overestimating the treatment benefit of both cemiplimab and pembrolizumab. As noted by Taylor et al. (2024),[38] the assumption of applying a waning on this 'immediate' basis

is that the treatment effect will disappear on a specific day, which is highly unlikely to reflect the underlying biology of the disease or the mechanism of action for IOs. Therefore, this approach appears to lack face validity and does not accord with the (albeit limited) clinical evidence. The EAG is of the opinion that applying a 'gradual' waning effect is more realistic. As noted by the company, in TA683 clinical input highlighted that a 'gradual' waning could be more clinically plausible.

As part of the EAG base case, the EAG have implemented a gradual linear waning effect for both PFS and OS starting at 24 months (in line with the stopping rule for both cemiplimab and pembrolizumab) and ending at 60 months, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed to be equal to the hazard for chemotherapy (HR vs chemotherapy = 1), in line with the assumptions made by the company in their base case. Like the company, the EAG has applied the same assumption for both cemiplimab and pembrolizumab. Using this 'gradual' treatment waning ensures that the continuation of treatment benefit due to T-cell activation is represented in the CEM but avoids the assumption of an 'immediate' treatment waning effect. The EAG are aware that, like the assumption of an 'immediate' waning effect, the assumption of a linear gradual waning effect is not evidence based and is unlikely to truly represent the underlying biology or disease or mechanism of action.[39] Further sensitivity analysis surrounding this assumption are presented as part of the EAG analysis.

4.2.6 Health-related quality of life

Table 4.7 summarises the EAG's critique on HRQoL within the economic model.

Table 4.7: Summary of EAG's critique on HRQoL

Analysis feature	Section in CS where methods are reported	EAG's assessment
HRQoL evidence used for health states in CEM	Section 3.4.1, p.139	**Some concerns** The EAG have some concerns around the utility values used in the CEM, in particular relating to the inherent uncertainty related to the use of mapping, the population used to map to the EQ-5D and the lack of scenario analysis. See Section 4.2.6.1 for further details.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Disutility for adverse effects	Section 3.4.5, p.154	**Some concerns** The disutility values for the AEs included in the CEM were identified from targeted reviews of previously published economic evaluations and HTA submissions. The EAG has some concerns regarding the AE data used in the CEM. See Section 4.2.6.2 for further comment.
Source: EAG outputs Abbreviations: AEs = adverse events; CEM = cost-effectiveness model; CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; AE = Adverse event		

4.2.6.1 HSUVs for the PF and PD health states

HSUVs were included in the CEM for the PF and PD health states (Table 4.8). The company assumed that because quality of life was linked to disease progression rather than treatment received, pooled values were used rather than treatment-specific utilities. Utility values were adjusted for age and sex using the approach suggested by Hernandez et al. (2022).[40] This was considered to be appropriate by the EAG.

Table 4.8: Utility values used in the CEM

Health states	Modelled average, mean (SE)
Progression-free	0.765 (0.005)
Progressed disease	0.723 (0.010)
Source: CS Document B, Table 44 Abbreviations: CEM = company economic model; SE = standard error	

As the EQ-5D was not collected in the EMPOWER-Lung 3 trial,[1] base case HSUVs were mapped from the oncology-specific EORTC-QLQ C30 using the algorithm from Longworth et al (2014),[41] which was identified by the company as being the most favourable out of those identified as part of a SLR. Although not explicitly stated in the CS, the EAG assumes that the response mapping algorithm from Longworth et al (2014) was the specific algorithm used. The EAG note that the specific choice of mapping algorithm from Longworth et al (2014) is unlikely to significantly impact the results. The mapping analysis was conducted using the EMPOWER Lung-3 ITT population (any PD-L1, any histology) population rather than the restricted population for which cemiplimab has a UK marketing authorisation (PD-L1 >1%, any histology), as the company argued that this allowed the use of all available data. The EAG note that this population does not align with the decision problem, although the impact on the results is likely to be minimal.

More generally, one of the principal limitations of predicting utility scores through mapping algorithms is that the predictive accuracy of the algorithm will be limited by the level of overlap between the two instruments in terms of what they attempt to measure. Given the significant differences between the condition-specific EORTC-QLQ C30 and the generic EQ-5D-3L, there is a degree of uncertainty related to the mapped utility estimates that remains unresolved.

Three alternative HSUVs available in the CEM are presented in Table 4.9. In the CS, the company state that sensitivity of the model to different utility values was tested by conducting scenario analyses using alternative published utility values. However, in the CS only the alternative utility values from TA584[42] are presented in as part of the scenario analysis, with the company arguing that *"only the utilities from Impower 150 are provided in Section B.3.8.3 as the other utility values from Table 44 also resulted in dominance for cemiplimab + chemotherapy"*. The EAG note that whilst the alternative utility values do result in dominance for cemiplimab + chemotherapy, the cost-effectiveness results presented in the CEM are not appropriate for decision making, as PAS prices are used for cemiplimab only, with list prices for other immunotherapies and chemotherapies. The EAG note that using the Nafees (2008)[43] utility values from TA584 has a significant impact on incremental QALYs, decreasing from [redacted] in the base case to [redacted]. The use of these alternative HSUVs is explored as part of the EAG scenario analysis.

In the CS, the company state that although four further sources were found during their SLR, these were not included in the cost-effectiveness analysis as they were from monotherapy studies *"which were indicated by UK clinical expert lung oncologists to be less representative of expected HSUV of IO + chemotherapy treatments"*. The EAG note that in the post-advisory board clarification questionnaire follow up provided in response to the PfCs,[5] Clinician 1 indicated that [redacted], however Clinician 2 and Clinician 3 indicated that [redacted]. The use of alternative utility values from IO monotherapy appraisals will be explored as part of the EAG analysis.

Table 4.9: Alternative HSUVs available in the CEM

Source	Response Status	Modelled average, mean (SE)
NICE TA584	Progression-free	0.710 (0.005)
	Progressed	0.690 (0.015)
NICE TA584 (Scenario Analysis)	Progression-free	0.673 (0.070)
	Progressed	0.473 (0.022)
NICE TA584 (Scenario Analysis)	Progression-free	0.710 (0.023)
	Progressed	0.670 (0.041)

Source: CS Document B, Table 44
Abbreviations: HSUVs = health-state utility values; TA = technology appraisal; CEM = company economic model; SE = standard error; CS = company submission

4.2.6.2 Disutility values for AEs

The disutility values for AEs used in the CEM are shown in Table 4.10. Frequencies of AEs were sourced from the EMPOWER-Lung 3 trial[1] for the cemiplimab + chemotherapy arm and the KEYNOTE-189[34] and KEYNOTE-407[35] trials for the pembrolizumab + chemotherapy arm (Table 4.11.11).

Table 4.10: Disutility values for AEs used in the CEM

Adverse event	Disutility	Source	Estimated QALY decrement
Anaemia	-0.125	Lloyd et al. (2008)[44], TA724[45]	-0.010
Fatigue	-0.073	Nafees et al. (2008),[43] TA724[45]	-0.006
Neutropenia	-0.090	Nafees et al. (2008),[43] TA724[45]	-0.007
Thrombocytopenia	-0.108	TA359[46] TA772[47]	-0.009

Source: CS Document B, Table 48
Abbreviations: CS = company submission; CEM= company economic model; AEs = adverse events; QALY = Quality-adjusted life year; TA = technology appraisal

Table 4.11: Proportions of AEs used in the CEM

Adverse event	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Anaemia	10.90%	17.65%
Fatigue	2.88%	6.38%
Neutropenia	6.41%	19.46%
Thrombocytopenia	3.21%	8.48%

Source: CS Document B, Table 43
Abbreviations: CS = company submission; CEM= company economic model; AEs = adverse events

The CEM assumed a 30-day duration to estimate the QALY decrement in line with the length of the model cycle, with these QALY decrements applied as a one-off decrement in the first cycle of the analysis. Although this assumption implies that all AEs are transitory (and that there are no persisting impacts of AEs on individuals over time), this is an assumption typically made in NICE TAR appraisals, for example TA802.[48] The EAG note that treatment-specific AE profiles are used in the CEM, despite the chemotherapy backbone regime being assumed to be the same across treatments. The clinical expert consulted by the EAG noted that the Grade 3+ AEs included in the model would almost exclusively be caused by the chemotherapy regime rather than IO. As noted by the company, this results in a "misalignment" between the AEs and chemotherapy regime. The company explored the impact of different AE regimes in their scenario analysis, with Scenario 13 (which excludes AE costs and disutilities) showing to have a small impact on the results. In the EAG base-case, the AEs are equalised across the treatment arms to avoid this

"misalignment". This also aligns with the clinical expert advice gathered by the company, which stated that [redacted] and that there was [redacted].

4.2.7 Resources and costs

Table 4.12.12 summarises the EAG's critique on resources and costs within the economic model.

Table 4.12: Summary of EAG's critique on resources and costs

Analysis feature	Section in CS where methods are reported	EAG's assessment
Drug acquisition costs	B.3.5.1, p.154	**Some Concerns** Drug acquisition and vial costs for all interventions were sourced from the BNF[31] and eMIT.[32] Concomitant medications and vial sharing were not included in the base-case; however, both have negligible impact on the cost effectiveness results. The EAG has some concerns regarding the distribution of chemotherapy regimes, as these were assumed to be the same for cemiplimab + chemotherapy and pembrolizumab + chemotherapy. See Section 4.2.7.1 for further details.
Administration costs	B.3.5.2, p.162	**Appropriate** Administration unit costs were sourced from the NHS reference costs[30] and applied to each treatment option in the model based on administration frequency and duration of time for delivering the regimen. The EAG find these assumptions to be appropriate.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Subsequent treatment costs	B.3.5.3, p.163	**Some Concerns** Following progression on first-line treatment, subsequent therapy costs were applied for patients in the post-progression health state. The EAG has some concerns regarding these subsequent treatment costs. See Section 4.2.7.2 for further details.
Routine care costs	B.3.5.4, p.167	**Appropriate** Resources and costs for routine disease management in the pre- and post-progression health states were also included in the CEM. The frequency of resource use was sourced from NICE TA531,[49] with the unit costs sourced from NHS reference costs and PSSRU unit costs.[30] Resource use was assumed to be identical for all therapies, and validated by UK clinical experts. The EAG find these assumptions to be appropriate.
End-of-life costs (terminal care costs)	B.3.5.5, p.169	**Appropriate** A one-off cost for end-of-life care was applied upon transition to the death health state, using assumptions from TA531 and costs from the PSSRU and NHS reference costs. The EAG considers these assumptions to be appropriate.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Adverse event costs	B.3.5.6, p.169	**Appropriate** Hospitalisation costs associated with the treatment of Grade 3+ AEs were sourced from the literature. Unit costs were derived from the NHS reference costs. The EAG checked the sources related to these costs and found them to be appropriate.

Source: EAG output
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NHS = National Health Service; TA = technology appraisal; BNF = British National Formulary; eMIT = drugs and pharmaceutical electronic market information tool; NICE = The National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit AEs = adverse events; CEM cost-effectiveness model

4.2.7.1 Drug acquisition costs

The distribution of chemotherapy regimens was assumed to be the same for cemiplimab + chemotherapy and pembrolizumab + chemotherapy, with this information gathered the from EMPOWER-Lung 3 trial[1] and applied to both treatment arms in the CEM. The EAG note that the use of chemotherapy was more flexible in EMPOWER-Lung 3 than in KEYNOTE-189[34] and KEYNOTE-407.[35] In the CS, the company state that this assumption is necessary to ensure that any drug cost differences in the model are due to the cost of IOs rather than heterogeneity in chemotherapy use across the clinical studies, with clinical experts consulted by the company confirming that this is a reasonable assumption. Despite this, the EAG note that the distribution of chemotherapy regimes is still a matter of uncertainty. However, the EAG also note that minor differences in the distribution of chemotherapy regimes are unlikely to have a significant impact on the results in the CEM. The EAG also note that the prices for the treatments included in the submission in Appendix K[8] differ to those presented in the main CS and the CEM. The EAG have used the prices provided in the main CS and CEM in the EAG analyses.

4.2.7.2 Subsequent Treatment Costs

Following progression on first-line treatment, subsequent therapy costs were applied for patients in the post-progression health state. The distribution of post-progression subsequent treatment is shown in Table 4.13.

Table 4.13: Distribution of post-progression subsequent treatment

Initial (pre-progression) treatment		
Post-progression treatment	**Cemiplimab + chemotherapy**	**Pembrolizumab + chemotherapy**
Immunotherapies		
Pembrolizumab	0.6%	0.6%
Nivolumab	0.0%	0.0%
Atezolizumab	0.3%	0.3%
Chemotherapies		
Docetaxel	4.5%	4.5%
Carboplatin	5.4%	5.4%
Cisplatin	1.9%	1.9%
Gemcitabine	3.5%	3.5%
Paclitaxel	3.2%	3.2%
Pemetrexed	1.9%	1.9%
Total	**21.5%**	**21.5%**

Source: CS Document B, Table 55
Please note that due to rounding, there are minor disparities between sum of the individual immunotherapies and chemotherapies percentages and total percentage of post-progression subsequent treatments.

As noted by the company, in the EMPOWER-Lung 3 trial the uptake of subsequent therapies was lower than anticipated, likely due to the relatively short follow-up in post-progression in the trial at the data cut-off date, and therefore the same post-progression distribution of subsequent therapy

was assumed for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. The EAG note that this uptake of subsequent therapies is significantly lower than in other IO studies for patients with NSCLC. For example, in the five-year data from the KEYNOTE-189 trial, 55.3% of those in the pembrolizumab + chemotherapy treatment had subsequent pharmacological therapy, with 25.4% having subsequent anti-PD-L1 therapy. Furthermore, in the five-year data from the KEYNOTE-407 trial, 39.2% of those in the pembrolizumab + chemotherapy arm had subsequent pharmacological therapy, with 11.9% having subsequent anti-PD-L1 therapy. Any underestimation in subsequent treatment rates will lead to an underestimation of the costs associated with subsequent treatments.

A scenario analysis (Scenario 9) was conducted by the company where subsequent treatment distributions sourced from the EMPOWER-Lung 3 trial were reweighted to align with the overall distribution for IO and other systemic therapies observed in KEYNOTE-189. This scenario analysis showed that the results insensitive to this alternative subsequent treatment distributions, with the incremental costs changing from [redacted] in the base case to [redacted]. The EAG has conducted additional scenario analysis using alternative subsequent treatment distributions obtained from the KEYNOTE-189 and KEYNOTE-407 studies.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company presented an incremental cost-effectiveness analysis and cost comparison (which assumed equal efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy) with the list price for pembrolizumab and a patient access scheme (PAS) price for cemiplimab. These results are not appropriate for decision making because confidential prices are not yet available for pembrolizumab, chemotherapy treatments and immunotherapies included in the CEM.

The company's base-case deterministic cost-effectiveness results using the PAS discount for cemiplimab is shown in Table 1.1 and Table 5.2. Table 5.1 shows the deterministic analysis for the MHRA population with PD-L1 > 1% NSCLC that responded to treatment with cemiplimab + chemotherapy. The analysis compares cemiplimab + chemotherapy and pembrolizumab + chemotherapy for this population and shows cemiplimab + chemotherapy dominating pembrolizumab + chemotherapy by decreasing the cost by [redacted] per patient; and increasing total QALYs by [redacted]. The net monetary benefit of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy for a willingness to pay threshold of £20,000 was [redacted] (see Table 5.2).

Table 5.1: Company base-case deterministic results for cemiplimab + chemotherapy vs pembrolizumab + chemotherapy, using the PAS price of cemiplimab

Technology	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£)
Cemiplimab + Chemotherapy	[redacted]	3.26	[redacted]				
Pembrolizumab + Chemotherapy	£126,144	2.93	2.15	[redacted]	0.33	[redacted]	Dominating

Source: CS Document B, Section 3.9.1

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYs = life years gained; PAS = Patient Access Scheme; QALY = quality-adjusted life year

Table 5.2: Net monetary benefit for company base-case deterministic results

Technology	Incremental costs (£)	Incremental QALY	ICER (£)	NMB at £20,000	NMB at £30,000
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Source: CS Model
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; NR = Not Reported

5.2 Company's sensitivity analyses

To explore uncertainty within their cost-effectiveness analysis, the company conducted a probabilistic sensitivity analysis over 1,000 iterations using the PAS price for cemiplimab. The company reported the following probabilistic sensitivity analysis (PSA) results showing cemiplimab + chemotherapy as the dominant intervention over pembrolizumab + chemotherapy and decreasing costs by [redacted] Table 5.3 and

Figure 5.1 show the probabilistic results reported by the company.

The EAG considers that the parametric distributions used to model uncertainty in the mean estimate were appropriate. The EAG verified that 1000 iterations for PSA in the model has low a sampling error.

Table 5.3: PSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab (company results)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Cemiplimab + Chemotherapy	[redacted]	[redacted]			

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Pembrolizumab + Chemotherapy	£126,224	2.16	[redacted]	[redacted]	Dominating

Source: CS Document B, Section B.3.8.1, Table 67

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.1: ICEP for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab

Source: CS Document B, Section B.3.8.1, Figure 31
Abbreviations: GBP = pounds sterling; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; ICEP = Incremental Cost-Effectiveness Plane

The EAG re-ran the PSA analysis in the same model file and obtained similar results. In the EAG's run, cemiplimab + chemotherapy was dominant compared to pembrolizumab + chemotherapy, with incremental QALYs of [redacted] and incremental costs of [redacted] The results obtained by the EAG are reported in Table 5.4 and Figure 5.2.

Table 5.4: PSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab (EAG results)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	126,186	2.17	[redacted]	[redacted]	Dominating

Source: CS Model, EAG Analysis
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: EAG re-run of ICEP for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab

Source: CS model, EAG Analysis
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICEP = incremental cost-effectiveness plane; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY =quality-adjusted life year

The base-case one-way sensitivity analysis (OWSA) presented by the company included the deterministic analysis of disease progression and survival parameters of NSCLC patients. The EAG considered these parameters to be informative and relevant to the analysis. These results are shown in Table 5.5 and Figure 5.3.

Table 5.5: OWSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Cemiplimab PFS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy PFS	[redacted]	[redacted]	[redacted]
Cemiplimab OS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy OS	[redacted]	[redacted]	[redacted]
Chemotherapy Curve PFS	[redacted]	[redacted]	[redacted]
Disease Management Cost - PD	[redacted]	[redacted]	[redacted]
Utility PD	[redacted]	[redacted]	[redacted]
Chemotherapy Curve OS	[redacted]	[redacted]	[redacted]
Disease Management Cost - PF	[redacted]	[redacted]	[redacted]
Utility PF	[redacted]	[redacted]	[redacted]

Source: CS Model
Abbreviations: CS = company submission; GBP = pounds sterling; ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

Figure 5.3: OWSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in net monetary benefit

Source: CS Model
Abbreviations: CS = company submission; GBP = pounds sterling; ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

The OWSA suggested that cemiplimab PFS was the largest determinant of cost-effectiveness. Other important parameters included the pembrolizumab + chemotherapy PFS, OS of cemiplimab, OS of pembrolizumab + chemotherapy and health state costs of NSCLC.

The results from the company's deterministic scenario analysis are shown in Table 5.6. In all scenarios aside from two, cemiplimab + chemotherapy remained dominant over pembrolizumab + chemotherapy. In Scenario 10, where the company applied a hypothetical discount of 65% to the pembrolizumab list price in a CUA, the ICER was reported as [redacted]. In Scenario 11, where the company applied the same hypothetical discount to the cost comparison analysis, there was an assumption of equal QALYs, with pembrolizumab + chemotherapy found to be cost saving compared to cemiplimab + chemotherapy.

The subgroup analyses explored the cost-effectiveness of cemiplimab + chemotherapy for subgroups based on histology and PD-L1 levels. As shown in

5.3 Subgroup analyses

Table 5**.7**, cemiplimab + chemotherapy dominated pembrolizumab + chemotherapy in all the subgroups except for the squamous subgroup with PD-L1 values ≥50%. For this subgroup, cemiplimab + chemotherapy was less costly and was less effective compared to pembrolizumab + chemotherapy.

Table 5.6: Deterministic scenario analysis results for the company base-case

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
	Company base-case	**N/A**	**N/A**	[redacted]	[redacted]	**Dominating**
1	Alternative PFS reference and two-step NMA	Log-logistic	Lognormal	[redacted]	[redacted]	Dominating
2	Alternative OS reference and two-step NMA	Log-logistic	Generalised gamma	[redacted]	[redacted]	Dominating
3	PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS	2-Step NMA	Constant HR	[redacted]	[redacted]	Dominating
4	Applying HRs to PFS to estimate time on treatment	Equal to PFS	HR applies to PFS	[redacted]	[redacted]	Dominating
5	Waning of treatment effect applied to PFS/OS from 36 months	60 months	36 months	[redacted]	[redacted]	Dominating
6	Waning of treatment effect applied to PFS/OS from 36 to 60 months	60 months	36 months	[redacted]	[redacted]	Dominating
7	Continuation of treatment effect (no waning applied)	Treatment waning effect applied	Extrapolation of HR trend	[redacted]	[redacted]	Dominating

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
8	Alternative health state utility values (NICE TA584 atezo+bev+chemo non-squamous IMpower 150 utilities using UK tariff)	EMPOWER LUNG 3 Trial, EORTC to EQ-5D-5L mapping	NICE TA584, Impower 150 utilities using UK tariff	[redacted]	[redacted]	Dominating
9	Subsequent treatment distribution	Subsequent treatment distribution from EMPOWER-LUNG 3 trial data	Alternative subsequent treatment distribution from KEYNOTE – 189 trial data	[redacted]	[redacted]	Dominating
10	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 0% in the cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	[redacted]	[redacted]	[redacted]
11	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	Hypothetical discount applied to pembrolizumab list price: 0% in the cost-utility analysis the cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	[redacted]	[redacted]	[redacted]
12	Alternative reference arm based on pooled KEYNOTE studies	EMPOWER Lung 3 Data	Pooled Keynote-189 and 407 data	[redacted]	[redacted]	Dominating

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
	(log-logistic for PFS and OS)					
13	Exclude AE costs and disutilities	AE costs and disutilities included	AE costs and disutilities excluded	[redacted]	[redacted]	Dominating
14	Assume no drug wastage	Drug Wastage included	No drug wastage	[redacted]	[redacted]	Dominating
15	Cemiplimab + chemotherapy patients receive AUC5 carboplatin instead of AUC6	Cemiplimab + chemotherapy patients receive AUC6 carboplatin	Cemiplimab + chemotherapy patients receive AUC5 carboplatin	[redacted]	[redacted]	Dominating
16	75% of pembrolizumab + chemotherapy patients switch to pembrolizumab monotherapy Q6W after 4-months of treatment	pembrolizumab + chemotherapy – 11% of patients pembrolizumab monotherapy-89%	pembrolizumab + chemotherapy – 25% of patients pembrolizumab monotherapy-75%	[redacted]	[redacted]	Dominating
17	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis	AE costs in the pembrolizumab + chemotherapy arm assumed equal to the EMPOWER-Lung 3 data in the cost-comparison analysis	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis	[redacted]	[redacted]	Equal QALY

Source: CS Document B.3.8.3, EAG Analysis
Abbreviations: AE = adverse event; PFS = progression-free Survival, OS = Overall Survival; NMA = Network-Meta Analysis; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality adjusted life years; HR = hazard ratio; NICE = National Institute of Health and Care Excellence;

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
TA = technology appraisal; AUC = area under the curve; AE = adverse event; Q6W = every 6 weeks; UK = Unites Kingdom; EORTC = European Organisation for Research and Treatment of Cancer						

5.4 Subgroup analyses

Table 5.7: Subgroup analysis results for the company base-case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Base case results (PD-L1 ≥1%, any histology)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,224	2.16	[redacted]	[redacted]	Dominating
PD-L1 1-49% squamous histology subgroup, assuming two-step NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£100,943	1.52	[redacted]	[redacted]	Dominating
PD-L1 1-49% squamous histology subgroup, assuming constant HR NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£100,948	1.53	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, squamous histology subgroup, assuming two-step NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£141,339	1.95	[redacted]	[redacted]	Less costs and less effective
PD-L1 ≥50%, squamous histology subgroup, assuming constant HR NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,319	1.76	[redacted]	[redacted]	Less costs and less effective
PD-L1 1-49% non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£118,961	2.14	[redacted]	[redacted]	Dominating
PD-L1 1-49% non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					

Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£113,968	2.11	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£143,608	2.10	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£130,765	1.70	[redacted]	[redacted]	Dominating

Source: CS Document B, Section B.3.8.4, Table 69
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; PFS = progression-free survival; PD-L1 = programmed death ligand 1; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival

5.5 Model validation and face validity check

The company submitted model validation was conducted using the relevant items of the CADTH Model Validation Tool.[50]

5.5.1 Face validity assessment and technical verification

The EAG several minor errors in the initially submitted CEM, which were corrected by the company. The EAG were unable to replicate one scenario from the company scenario analyses in the subsequently submitted CEM; however, this issue was addressed by the company and EAG as part of the Factual Accuracy Check. The face validity and the technical verification of the model was found to be satisfactory by the EAG.

5.5.2 Comparisons with external data

In the survival analysis, the different parametric distributions were assessed for predictive accuracy with landmark survival estimates. For the chemotherapy PFS, the predictions from the different parametric models were compared with the two-year landmark PFS and median PFS from the EMPOWER-Lung 3 trial.[1]For the chemotherapy OS, the predictions from the different parametric distributions were compared with the five-year survival rates taken from several relevant previous studies, including four NICE submissions.[34-37,45,51] For the pembrolizumab + chemotherapy OS, the predictions from the different parametric distributions were also compared with the survival rates from several relevant previous studies, including NICE submission.[33-35,37]

As well as comparing the predictions to landmark survival estimates, the company also validated their preferred extrapolations for both PFS and OS with UK clinical expert lung oncologists at an advisory board and post-advisory board clarification questionnaire follow up.[5] As the same advisory board meeting, a number of other aspects of the CS were discussed and validated, including the treatment waning assumptions, adverse events, utilities and chemotherapy regimens.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case. This EAG base-case included several adjustments to the company base-case presented in Section **Error! Reference source not found.**. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016):[52]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below.

Fixing errors

Some minor errors were identified by the EAG following the original submission of the CEM; however, these errors were corrected by the company prior to the PfCs.

Fixing violations

No violations to the NICE reference case were identified by the EAG.

Matters of judgement

Although there are questions surrounding the population eligible to receive cemiplimab + chemotherapy (Key Issue 1) and the comparators included in the company's decision problem not reflecting all of the treatments in the NICE scope (Key Issue 2), the EAG were unable to incorporate these issues into the EAG base case.

6.1.1.1 Equal ToT rates across treatment arms

In the company base case, the company assume that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. As stated in Section 4.2.4, the EAG note that by assuming that the assumptions that ToT is equal to PFS ignores the fact that ToT has an impact on PFS and OS in the clinical trials that provide the evidence, and that assuming that ToT is equal PFS will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy.

For consistency in the CEM, the estimates of ToT should either be estimated from the respective clinical trials or both effectiveness estimates and ToT should be assumed to be equal. As noted by the company, the EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond disease progression under certain conditions, resulting in patients being treated beyond the 24-month stopping rule, and a HR or ToT relative to PFS of 1.17. The corresponding HR of ToT for pembrolizumab was 0.84, calculated from the

KEYNOTE-407[35] and KEYNOTE-189[34] trials and weighted by the split of squamous and non-squamous patients in EMPOWER-Lung 3[1]. Clinical advisors consulted by the company noted that the discrepancies in the ToT between the between cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms "*might be due to IO experience bias or reporting variations between trials"*. In the EAG base-case, the HRs of ToT estimated from EMPOWER-Lung 3 for cemiplimab + chemotherapy and KEYNOTE-407 and KEYNOTE-189 for pembrolizumab are used for consistency in the CEM. This aligns with Scenario 4 from the CS.

6.1.1.2 Assumption of a 'gradual' treatment waning beginning at 24 months

In the company base case, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which the estimated hazard of both disease progression and death is assumed to be equal to chemotherapy at five years for both PFS and OS. The EAG is concerned that the assumption of an 'immediate' waning effect after five years in the company base case is overestimating the treatment benefit of both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. As noted in Section 4.2.5, the EAG is of the opinion that applying a 'gradual' waning effect is more realistic than an 'immediate' waning at a specified time point.

In the EAG base, a gradual linear waning effect for both PFS and OS starting at 24 months (in line with the stopping rule for both cemiplimab and pembrolizumab) and ending at 60 months is used, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed to be equal to the hazard for chemotherapy. It is worth noting that Scenario 5 from the CS applies a treatment effect to PFS/OS from 36 months. The scenario is replicated on the EAG base case as part of the EAG scenario analyses.

6.1.1.3 *Equal AE rates across treatment arms*

In the company base case, treatment-specific AE profiles are used, despite the chemotherapy backbone regime being assumed to be the same across treatments. The clinical expert consulted by the EAG noted that the Grade 3+ AEs included in the model would almost exclusively be caused by the chemotherapy regime rather than IO. As noted by the company, this results in a "misalignment" between the AEs and chemotherapy regime. Clinical expert advice gathered by the company stated that [redacted] and that there was [redacted].

In the EAG base, the AE profile for pembrolizumab + chemotherapy has been applied to both treatment arms. It is worth noting that Scenario 13 from the CS removes excludes AEs and their associated costs from the CEM. The scenario is replicated on the EAG base case as part of the EAG scenario analyses. The EAG has not included a scenario where AE rates are trial-specific and the chemotherapy backbone regime are trial-specific; that scenario would also be consistent. The results are not expected to be very different given the low cost of chemotherapy.

6.1.2 EAG exploratory scenario analyses

The EAG performed scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case. As well as replicating the company scenario analysis on

the EAG base case (**Error! Reference source not found.**) and the company sub-group analysis on the EAG base-case (**Error! Reference source not found.**), the EAG conducted some additional analyses (**Error! Reference source not found.**), detailed below.

- Additional Scenario 1 - Alternative subsequent therapy distributions based on KEYNOTE-407

In this additional scenario, the subsequent therapy distributions for both treatment arms were inflated to be in line with the subsequent therapies observed in the pembrolizumab + chemotherapy arm in the five-year outcomes from the KEYNOTE-407 trial. In this study, 39.2% of patients received any subsequent pharmacological therapy, with 11.9% of patients receiving any subsequent anti-PD(L)1 therapy. As shown in Table 6.1, the total immunotherapies were inflated to equal 11.9%, and the total chemotherapies were inflated to equal 27.3% (39.2% minus 11.9%). Once more, the proportions of immunotherapies and chemotherapies within these inflated totals were assumed to be equal to those from the EMPOWER-Lung 3 trial.

Table 6.1: Alternative post-progression treatment distributions

Post-progression treatment	Company Base Case	Company Scenario 9	EAG Additional Scenario 1	EAG Additional Scenario 2
Immunotherapies				
Pembrolizumab	0.6%	16.9%	7.9%	25.4%
Nivolumab	0.0%	0.0%	0.0%	0.0%
Atezolizumab	0.3%	8.5%	4.0%	0.0%
Immunotherapies Total	1.0%	25.4%	11.9%	25.4%
Chemotherapies				
Docetaxel	4.5%	6.5%	6.0%	6.5%
Carboplatin	5.4%	7.9%	7.3%	7.9%
Cisplatin	1.9%	2.8%	2.6%	2.8%
Gemcitabine	3.5%	5.1%	4.7%	5.1%
Paclitaxel	3.2%	4.7%	4.3%	4.7%
Pemetrexed	1.9%	2.8%	2.6%	2.8%
Chemotherapies Total	20.5%	29.9%	27.3%	29.9%
Immunotherapies + Chemotherapies Total	**21.5%**	**55.3%**	**39.2%**	**55.3%**

Source: CS Document B, Table 55
Abbreviations: EAG = Evidence Assessment Group
Please note that due to rounding, there are minor disparities between sum of the individual immunotherapies and chemotherapies percentages and total percentage of post-progression subsequent treatments.

- Additional Scenario 2 – Alternative subsequent therapy distributions based on KEYNOTE-189 with no atezolizumab

This additional scenario is identical to Company Scenario 9, with the exception that all patients prescribed subsequent immunotherapy are assumed to receive pembrolizumab, with no patients receiving atezolizumab. Clinical expert gathered by the EAG noted that in her experience atezolizumab is very rarely given in this population. Furthermore, as noted by the company, atezolizumab is only available for use in people with non-squamous disease and PD-L1 1-49% and has an 8% market share in that population.

- Additional Scenario 3 – Alternative approach to calculating subsequent therapy cost

In this additional scenario, the EAG calculated the subsequent treatment costs in a different way, by assuming 20% people who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences disease progression. In the company base-case, it was calculated by assuming that the cost of subsequent treatment was distributed over time according to the percentage of the cohort in the progressive disease state in a given cycle. This percentage of the cohort is a cumulative percentage of the cohort in the progressive disease state over time, where the cycle person-time is a proportion of the total person-time across cycles. As an alternative approach, the EAG has assumed that a percentage of patients who died did so in the progression-free state. The full cost of the subsequent treatment course was incurred for every patient who experienced disease progression over relevant months following disease progression.

- Additional Scenario 4 - Alternative approach to calculating subsequent therapy cost

In this additional scenario, the subsequent treatment distribution from KEYNOTE-189 trial from Company Scenario 9 is applied with the EAG Additional Scenario 3 method of calculating the cost of subsequent treatment in a different way, to the EAG base-case.

- Additional Scenario 5 – Alternative approach to calculating subsequent therapy cost

This additional scenario is identical to EAG Additional Scenario 3, in which the EAG calculated the subsequent treatment costs in a different way but it was assumed that 5% of patients who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences disease progression.

- Additional Scenario 6 – Alternative approach to calculating subsequent therapy cost

In this additional scenario, the subsequent treatment distribution from the KEYNOTE-189 trial from Company Scenario 9 is applied with the EAG Additional Scenario 5 method of calculating the cost of subsequent treatment in a different way, to the EAG base-case.

- Additional Scenario 7 - Generalized gamma distribution for PFS

In this additional scenario, the parametric distribution for PFS was changed to Generalized gamma. As described in Section 4.2.3, this distribution had the most accurate estimates of two-year PFS based on the landmark survival at two years for both cemiplimab +

chemotherapy (23.2%) and pembrolizumab + chemotherapy (25.0%) from the EMPOWER-Lung 3 trial and KEYNOTE-189 and KEYNOTE-407.

- Additional Scenario 8 - Gamma distribution for OS

In this additional scenario, the parametric distribution for OLS was changed to gamma. As described in Section 4.2.3, this distribution had the lowest AIC and second lowest BIC.

- Additional Scenario 9 - Generalized gamma distribution for PFS, gamma distribution for OS

This scenario is a combination of Additional Scenario 8 and Additional Scenario 9

- Additional Scenario 10 - Alternative utility values for PFS and Post-Progression from Nafees et al (2008)

In this additional scenario, the alternative utility values for PFS (0.673) and Post-Progression (0.473) from Nafees et al (2008)[43] were used. These utility values were discussed by the company in the CS, but not included in the company scenario analyses.

- Additional Scenario 11 - Alternative utility values for PFS and Post-Progression from Chouaid et al (2013)

In this additional scenario, the alternative utility values for PFS (0.710) and Post-Progression (0.670) from Chouaid et al (2013)[53] were used. These utility values were discussed by the company in the CS, but not included in the company scenario analyses.

6.1.3 EAG subgroup analyses

No additional subgroup analyses were conducted by the EAG.

6.2 Impact on the ICER of additional analyses undertaken by the EAG

6.2.1 The EAG base-case

The EAG base-case was presented in Section 6.1.1. Table 6.2 reports the individual impact of the changes proposed by the EAG to generate the EAG base-case results. Appendix 1 explains how the changes were implemented in the CEM.

Table 6.2: Deterministic and probabilistic EAG base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
CS base-case – Deterministic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,144	2.15	[redacted]	[redacted]	Dominating
CS base-case – Probabilistic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,224	2.16	[redacted]	[redacted]	Dominating
Matter of Judgement 1: Treatment Waning					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£125,857	2.10	[redacted]	[redacted]	Dominating
Matter of Judgement 2: Time on Treatment					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,751	2.15	[redacted]	[redacted]	Dominating
Matter of Judgement 3: Adverse Events same as Pembrolizumab + Chemotherapy					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,144	2.15	[redacted]	[redacted]	Dominating
EAG base-case (matters of judgment 1-3) – Deterministic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,476	2.10	[redacted]	[redacted]	Dominating
EAG base-case (matters of judgment 1-3) – Probabilistic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,595	2.11	[redacted]	[redacted]	Dominating

Source: EAG Analysis
Abbreviations: ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year
*All ICERs are for cemiplimab + chemotherapy

The change in assumptions regarding treatment waning had little impact on the costs, but had a significant impact on QALYs, changing the incremental QALYs from [redacted] in the company base-case to [redacted] in the EAG base-case. The change in assumptions regarding time on treatment had no impact on QALYs, but had a significant impact on costs, changing the incremental costs from [redacted] in the company base-case to [redacted] in the EAG base-case. The changes in assumptions regarding adverse events had little impact on either the costs or QALYs. In all cases, cemiplimab + chemotherapy remained the dominant strategy. These results are not appropriate for decision making, as a PAS price is used for cemiplimab only, with list prices for other immunotherapies and chemotherapies. Results using the confidential PAS prices for other immunotherapies and chemotherapies will be presented in the confidential PAS appendix.

6.2.2 Probabilistic sensitivity analysis

The estimated probabilistic results from the EAG base-case suggest that cemiplimab + chemotherapy dominates pembrolizumab + chemotherapy. Incremental QALYs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy were [redacted] and incremental costs were [redacted] The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

The incremental cost-effectiveness plane showing the incremental costs and QALYs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is presented in **Error! Reference source not found.**. The cost-effectiveness acceptability curves for cemiplimab + chemotherapy and pembrolizumab + chemotherapy are presented in **Error! Reference source not found.**

[redacted]

Figure 6.1 Incremental cost-effectiveness plane (EAG base-case)

Source: EAG's base-case economic model
Abbreviations: QALY = Quality-adjusted life years

Figure 6.2 Cost-effectiveness acceptability curve (CEACs) (EAG base-case)

Source: EAG base-case economic model
Abbreviations: QALY = Quality-adjusted life years

6.2.3 One-way sensitivity analysis

The results from the one-way sensitivity analysis and its impact on the net monetary benefit in the EAG base-case are shown in Table 6.3 and displayed graphically in **Error! Reference source not found.**. The most influential parameters in the deterministic OWSA were pembrolizumab + chemotherapy PFS, chemotherapy curve PFS, cemiplimab PFS and cemiplimab OS.

Table 6.3: One-way sensitivity analysis on EAG base-case with net monetary values

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Cemiplimab PFS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy PFS	[redacted]	[redacted]	[redacted]
Cemiplimab OS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy OS	[redacted]	[redacted]	[redacted]
Chemotherapy curve PFS	[redacted]	[redacted]	[redacted]

Disease management cost - PD	[redacted]	[redacted]	[redacted]
Utility PD	[redacted]	[redacted]	[redacted]
Chemotherapy curve OS	[redacted]	[redacted]	[redacted]
Disease management cost - PF	[redacted]	[redacted]	[redacted]
Utility PF	[redacted]	[redacted]	[redacted]

Source: EAG base-case Model
Abbreviations: ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

Figure 6.3 One-way sensitivity analysis with net monetary values

Source: EAG base-case economic model
Abbreviations: ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

6.2.4 Company deterministic sensitivity analyses on the EAG base case

The results from the company deterministic sensitivity analysis and their impact on the cost-effectiveness results are shown in **Error! Reference source not found.**. The scenarios that impacted the incremental costs the most were scenarios 10 and 11, in which a discount in price is assumed for the pembrolizumab cost. The scenario that impacted the incremental

QALYs the most was scenario 7 where no treatment waning effect is assumed. The use of alternative health utility values in scenario 8 also had significant impact on the total QALY.

Table 6.4 Company deterministic scenario analyses on EAG base-case

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	EAG base-case	**N/A**	[redacted]	[redacted]	**Dominating**
1	PFS reference and 2-step NMA (log-logistic)	Alternative PFS reference and 2-step NMA (log-normal)	[redacted]	[redacted]	Dominating
2	OS reference and two-step NMA (log-logistic)	Alternative OS reference and two-step NMA (generalised gamma)	[redacted]	[redacted]	Dominating
3	PFS 2-step NMA (log-logistic)	PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS	[redacted]	[redacted]	Dominating
4	Applying the same HRs to PFS to estimate time on treatment	Applying different HRs to PFS to estimate time on treatment	[redacted]	[redacted]	Dominating
5	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Waning of treatment effect applied to PFS/OS from 36 months	[redacted]	[redacted]	Dominating
6	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Waning of treatment effect applied to PFS/OS from 36 to 60 months	[redacted]	[redacted]	Dominating
7	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Continuation of treatment effect (no waning applied)	[redacted]	[redacted]	Dominating
8	Health state utility values (EMPOWER-Lung 3 trial,	Alternative health state utility values (NICE TA584 atezo+bev+chemo non-	[redacted]	[redacted]	Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	EORTC to EQ-5D-5L mapping (UK tariff, modelled average)	squamous IMpower 150 utilities using UK tariff)			
9	Subsequent treatment distribution from EMPOWER-LUNG 3 trial data	Alternative subsequent treatment distribution from KEYNOTE – 189 trial data	[redacted]	[redacted]	Dominating
10	Discount applied to pembrolizumab list price is 0%	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	[redacted]	[redacted]	[redacted]
11	Discount applied to pembrolizumb list price is 0% in cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	[redacted]	[redacted]	Increased cost in cost-comparison analysis
12	Reference arm based on EMPOWER-Lung 3 data	Alternative reference arm based on pooled KEYNOTE studies (log-logistic for PFS and OS)	[redacted]	[redacted]	Dominating
13	AE costs and disutilities included	Exclude AE costs and disutilities	[redacted]	[redacted]	Dominating
14	Assume drug wastage	Assume no drug wastage	[redacted]	[redacted]	Dominating
15	Cemiplimab + chemotherapy patients receive AUC6 carboplatin	Cemiplimab + chemotherapy patients receive AUC5 carboplatin instead of AUC6	[redacted]	[redacted]	Dominating
16	pembrolizumab + chemotherapy – 11% of patients pembrolizumab monotherapy- 89%	75% of pembrolizumab + chemotherapy patients switch to pembrolizumab monotherapy Q6W after 4-months of treatment	[redacted]	[redacted]	Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
17	AE costs in the pembrolizumab + chemotherapy arm assumed equal to the EMPOWER-Lung 3 data in the cost-comparison analysis	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis (instead of assuming equal to EMPOWER-Lung 3)	[redacted]	[redacted]	Cost saving in a cost-comparison analysis.

Source: EAG base-case Model
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year, AE = adverse events; PFS = progression-free survival; NMA = network meta-analysis; OS = overall survival; TA – technology appraisal; HR = hazard ratio; EORTC = The European Organisation for Research and Treatment of Cancer; AUC = area under the curve
*All ICERs are for cemiplimab + chemotherapy

6.2.5 EAG additional deterministic sensitivity analysis

The results from the additional deterministic sensitivity analysis conducted by the EAG on the EAG base-case are shown in Table 6.5. Appendix 1 explains how the changes needed to generate these scenarios were implemented in the CEM. As shown, all additional scenarios conducted by the EAG in relation to the subsequent treatments (Additional Scenarios 1-7) made very little difference to the incremental costs and incremental QALYs. As shown in Additional Scenario 9 and Additional Scenario 10, using a gamma distribution as the OS reference curve (for chemotherapy) in the survival analysis decreases the incremental QALYs substantially, from [redacted] in the EAG base-case to [redacted]. As shown in Additional Scenario 11, using the alternative utility values from Nafees et al 2008[43] decreases the incremental QALYs substantially; however, the EAG note that both the absolute values and decrement between these utility values can be considered extreme.

Table 6.5: EAG Additional Scenario Analyses on EAG base-case

Additional Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	EAG base-case	**N/A**	[redacted]	[redacted]	**Dominating**
1	Subsequent therapy distributions based on EMPOWER-Lung 3	Alternative subsequent therapy distributions based on KEYNOTE-407	[redacted]	[redacted]	Dominating
2	Subsequent therapy distributions based on EMPOWER-Lung 3	Alternative subsequent therapy distributions based on KEYNOTE-189; pembrolizumab is assumed to the only immunotherapy used	[redacted]	[redacted]	Dominating
3	Cost of subsequent therapy is distributed over time as a percentage of the cumulative percentage of cohort in the progressive disease state over time	Alternative approach to calculating subsequent therapy cost, by assuming 20% people who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences	[redacted]	[redacted]	Dominating

Additional Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
		disease progression			
4	Subsequent treatment distribution from EMPOWER LUNG-3 trial with cost of subsequent therapy distributed over time as a percentage of the cumulative percentage of cohort in the progressive disease state over time	Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (20% people who died were in disease-free state)	[redacted]	[redacted]	Dominating
5	Cost of subsequent therapy is distributed over time as a percentage of the cumulative percentage of cohort in the progressive disease state over time	Alternative approach to calculating subsequent therapy cost, by assuming 5% people who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences disease progression	[redacted]	[redacted]	Dominating
6	Subsequent treatment distribution from EMPOWER LUNG-3 trial with cost of subsequent therapy distributed over time as a percentage of the cumulative	Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (5% people who died were in disease-free state)	[redacted]	[redacted]	Dominating

Additional Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	percentage of cohort in the progressive disease state over time				
7	PFS reference and 2-step NMA (log-logistic)	PFS reference and 2-step NMA (Generalized gamma)	[redacted]	[redacted]	Dominating
8	OS reference and 2-step NMA (log-logistic)	OS reference and 2-step NMA (gamma)	[redacted]	[redacted]	Dominating
9	PFS and OS reference and 2-step NMA (log-logistic)	Generalized gamma distribution for PFS + gamma distribution for OS	[redacted]	[redacted]	Dominating
10	PFS/OS utilities from EMPOWER-Lung 3 trial, mapped from EORTC to EQ-5D-5L	Alternative utility values for PFS/OS from Nafees et al (2008)	[redacted]	[redacted]	Dominating
11	PFS/OS utilities from EMPOWER-Lung 3 trial, mapped from EORTC to EQ-5D-5L	Alternative utility values for PFS/OS from Chouaid et al. (2013), UK tariff (scenario in TA 584)	[redacted]	[redacted]	Dominating

Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; PFS = progression-free survival; OS = overall survival; EORTC = European Organisation for. Research and Treatment of Cancer
*All ICERs are for cemiplimab + chemotherapy

6.2.6 Sub-group analysis

The subgroup analysis was conducted on the EAG base-case and is given in Table 6.6. The results showed that cemiplimab + chemotherapy was dominant (less costly and more effective) than pembrolizumab + chemotherapy in all the subgroups except the squamous population. In the patients with squamous NSCLC with PD-L1 ≥ 50%, the intervention was less costly and less effective when compared to the comparator.

Table 6.6: Subgroup analysis on EAG base-case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER* (£)
Base case results (PD-L1 ≥1%, any histology)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	**£116,476**	**2.10**	[redacted]	[redacted]	**Dominating**
PD-L1 1-49% squamous histology subgroup, assuming two-step NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£90,412	1.45	[redacted]	[redacted]	Dominating
PD-L1 1-49% squamous histology subgroup, assuming constant HR NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£90,815	1.46	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, squamous histology subgroup, assuming two-step NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£133,169	1.91	[redacted]	[redacted]	Less costly and less effective
PD-L1 ≥50%, squamous histology subgroup, assuming constant HR NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£106,956	1.71	[redacted]	[redacted]	Less costly and less effective
PD-L1 1-49% non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£108,597	2.04	[redacted]	[redacted]	Dominating
PD-L1 1-49% non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£103,416	1.97	[redacted]	[redacted]	Dominating

PD-L1 ≥50%, non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£143,901	2.10	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£130,226	1.61	[redacted]	[redacted]	Dominating

Source: EAG base-case model
Abbreviations: EAG = Evidence Assessment Group, ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; PD-L1 = programmes death ligand 1; OS = overall survival; NMA = network meta-analysis; HR = hazard ratio; PFS = progression-free survival
*All ICERs are for cemiplimab + chemotherapy

6.3 Overall conclusions of the EAG's cost-effectiveness analysis

The estimated probabilistic results from the EAG base-case suggest that cemiplimab + chemotherapy dominates pembrolizumab + chemotherapy using the PAS price for cemiplimab and the list prices for other immunotherapies and chemotherapies. Incremental QALYs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy were [redacted], and incremental costs were [redacted]. The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Using the HRs of ToT estimated from the EMPOWER-Lung 3, KEYNOTE-407 and KEYNOTE-189 clinical trials in the EAG base-case rather than assuming ToT was equal to PFS had no impact on incremental QALYs, but had a significant impact on incremental costs, changing the incremental costs from [redacted] in the deterministic company base-case to [redacted] in the deterministic EAG base-case. Assuming a "gradual" treatment waning beginning at 24 months and ending at 60 months in the EAG base-case rather than a continuation of the treatment effect to 60 months followed by an "immediate" waning had little impact on the incremental costs, but had a significant impact on incremental QALYs, changing the incremental QALYs from [redacted] in the deterministic company base-case to [redacted] in the deterministic EAG base-case. The changes in assumptions regarding adverse events had little impact on either incremental costs or incremental QALYs.

The most influential parameters in the deterministic OWSA were pembrolizumab + chemotherapy PFS, chemotherapy curve PFS, cemiplimab PFS and cemiplimab OS. In the company deterministic scenario analyses, the scenarios that impacted the incremental costs the most were scenarios 10 and 11, in which a discount in price was assumed for the

pembrolizumab cost. The scenario that impacted the incremental QALYs the most was scenario 7, where no treatment waning effect is assumed.

From the EAG additional scenario analyses, the scenarios related to subsequent treatments made very little difference to the incremental costs and incremental QALYs. Using a gamma distribution as the OS reference curve (for chemotherapy) in the survival analysis decreased the incremental QALYs substantially, from [redacted] in the EAG base-case to [redacted]. Using the alternative utility values from Nafees et al 2008[43] decreases the incremental QALYs substantially.

The subgroup analysis showed that cemiplimab + chemotherapy was dominant in all subgroups except in patients with squamous NSCLC with PD-L1 ≥ 50%, in which cemiplimab + chemotherapy was less costly and less effective than pembrolizumab + chemotherapy.

Once more, it is worth emphasising these results are not appropriate for decision making as a PAS price is used for cemiplimab only, with list prices for other immunotherapies and chemotherapies. Results using the confidential PAS prices for other immunotherapies and chemotherapies will be presented in the confidential PAS appendix.

6.4 Overall conclusions of the EAG's critique

The company conducted three SLRs focusing on clinical effectiveness, cost effectiveness, and HRQoL respectively. The EAG judged the methods of the SLRs to be broadly appropriate, with the following caveats. The search strategy was well reported and thorough, although published filters had been edited before use. The EAG explored some issues around the eligibility criteria and concluded that there were no major concerns. To estimate the relative efficacy of cemiplimab the authors conducted a 2-step NMA, fitting parametric models for PFS and OS across all the arms of all the studies included in the NMA analyses, running the NMA analyses to estimate the scale and shape parameters for each outcome statistic and selecting the best fitting model. The results from the NMA indicated comparable effectiveness between cemiplimab + chemotherapy compared to pembrolizumab + chemotherapy overall, although with very wide credible intervals. The EAG noted greater uncertainty around the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group for PFS as the estimate favoured pembrolizumab + chemotherapy in this population, again with wide credible intervals. The company stated that the relevant effect modifiers were not reported in the comparator studies at the relevant time points, in particular the % of patients receiving immunotherapy as a subsequent treatment, and consequently there is the potential for bias in the OS effectiveness estimate in favour of cemiplimab.

The company conducted a SLR with searches aimed at identifying cost-effectiveness studies, HRQoL and cost and resource use data to inform the economic model. These searches were considered fit for purpose; however, the EAG had some minor concerns regarding the HRQoL study type filter used by the company.

The EAG is concerned that the CS did not meet the NICE scope in two key areas. Firstly, the company included the PD-L1 ≥50%, squamous population despite the standard of care for this population sub-group being IO monotherapy. After querying this issue with the company in the PfCs and with the clinical advisor to the EAG, the EAG concludes that the PD-L1 ≥50%, squamous population sub-group is relevant as IO + chemotherapy would be the standard of care first line treatment for this population sub-group when urgent clinical intervention is needed (e.g., when the disease is progressing rapidly). Secondly, the company only included one comparator (pembrolizumab + chemotherapy) despite multiple treatments being included in the NICE scope. However, the EAG's clinical advisor agree that pembrolizumab + chemotherapy is the relevant comparator. The EAG has raised both points as key issues to highlight to the NICE committee that cemiplimab+ chemotherapy should only be administered to patients who would otherwise have received pembrolizumab + chemotherapy.

The first key issue the EAG raised regarding the economic analysis was the uncertainty in the assumptions regarding treatment discontinuation. The CEM assumed that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, guided by an advisory board meeting where advisors were cautious about concluding discrepancies between the between cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms. The EAG was concerned that by assuming that ToT is equal PFS, this will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy. In the EAG base case, the hazard rates from EMPOWER-Lung 3 and KEYNOTE-407 are used to estimate time on treatment.

The second key issue the EAG raised regarding the economic analysis was the uncertainty in the treatment waning assumptions made in the CEM. In the CEM, the company have assumed that there is an “immediate” waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy at 60 months. The EAG are concerned that applying waning on this “immediate” basis does not reflect the mechanism of action of Ios, lacks face validity and may be overestimating the treatment benefit of both cemiplimab and pembrolizumab. The EAG are of the opinion that a “gradual” waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy may be more appropriate. In the EAG base case, a “gradual” treatment waning has been applied, beginning at 24 months (in line with the stopping rule for both treatment) and ending at 60 months.

The EAG had some concerns regarding the utility values used by the company for the PF and PD and the AE profiles used to incorporate AE disutilities in the CEM, however overall the approach to HRQoL in CS was considered fit for purpose.

The EAG had some concerns regarding the drug acquisition and subsequent treatment costs, however overall the approach taken to calculate costs and resource use in the CS was considered fit for purpose.

The company considered that this condition did not meet the disease severity modifier criteria.

The company base-case suggested that, after applying the PAS discount to the unit cost of cemiplimab, cemiplimab + chemotherapy was the dominant strategy over pembrolizumab + chemotherapy, increasing QALYs by [redacted] and decreasing costs by [redacted] in the probabilistic analysis, with a [redacted] probability of being cost-effective at a £20,000 threshold and a [redacted] probability of being cost-effective at a £30,000 threshold.

The EAG found no errors in the CEM after an initial revision by the company. The EAG base-case changed the assumptions regarding treatment waning to allow for a “gradual” rather than “immediate” waning, changed the assumptions for estimating time on treatment and equalised the adverse event profiles across the treatment arms. The EAG base-case suggested that, after applying the PAS discount to the unit cost of cemiplimab, cemiplimab + chemotherapy was the dominant strategy over pembrolizumab + chemotherapy by increasing QALYs by [redacted] and decreasing cost by [redacted], with a [redacted] probability of being cost-effective at a £20,000 threshold and a [redacted] probability of being cost-effective at a £30,000 threshold.

The choice of parametric survival model for OS, the assumption related to treatment discontinuation and the assumption related to treatment waning were found by the EAG to be the parameters with the largest impact on the cost-effectiveness results. Further structural scenarios were tested using scenario analyses proposed by the EAG and recreating scenarios from the CS on the EAG base-case, with cemiplimab + chemotherapy remaining dominant over pembrolizumab + chemotherapy the vast majority of scenarios when using the PAS price for cemiplimab. The significant uncertainties from the NMA mean that the cost-effectiveness analysis is also subject to substantial uncertainty.

The company subgroup analyses explored the cost-effectiveness of cemiplimab + chemotherapy for subgroups based on histology and PD-L1 levels. Results showed that cemiplimab + chemotherapy dominated pembrolizumab + chemotherapy in all the subgroups, with the exception of the squamous subgroup with PD-L1 values ≥50%. For this subgroup,

cemiplimab + chemotherapy was less costly and was less effective compared to pembrolizumab + chemotherapy. The EAG note that these subgroup analyses are subject to considerable uncertainty.

7 APPENDIX 1 - GENERATING THE EAG BASE-CASE AND EAG ADDITIONAL SCENARIO ANALYSIS

Generating the EAG's base-case analysis

The EAG's base-case model was built upon the company's base-case model. The changes made on the model are given below.

1. *Equal time on treatment rates across treatment arm*

In the 'Input_Efficacy TTD' sheet, change cells F7 and F9 from 'Equal to PFS' to 'HR applied to PFS'.

2. *Assumption of a 'gradual' treatment beginning at 24 months*

In the 'Input_Efficacy_OS' and 'Input_Efficacy_PFS' sheets, change cells F29 and F31 from '60' to '24'.

3. *Equal adverse event rates across treatment arm*

In 'Input_Safety_Tx' sheet, paste the array E12:E22 into array C12:C22.

Generating the EAG's additional scenario analyses

The EAG's additional scenario analyses was built upon the EAG base-case. The changes needed to generate the EAG's additional scenario analyses are given below.

1. *EAG Additional Scenario 1: Subsequent treatment distribution from the KEYNOTE – 407 trial applied to both the treatment arms:*

In the 'Input_Drug_Post_Prog' sheet, arrays C15:C17 and E15:E17 inflated by a factor of 11.9/SUM(C15:C17), and arrays C25:C30 and E25:E30 inflated by a factor of 27.3/SUM(C25:C30).

2. *EAG Additional Scenario 2: Subsequent treatment distribution from KEYNOTE – 189 trial applied to both the treatment arms, with pembrolizumab being the only alternative therapy immunotherapy considered.*

In the 'Input_Drug_Post_Prog' sheet, cells C15 and E15 changed to 25.4%, cells C17 and E17 changed to 0%, and arrays C25:C30 and E25:E30 inflated by a factor of 29.9/SUM(C25:C30).

3. *EAG Additional Scenario 3: Alternative approach to calculating the cost of subsequent therapy. Assume that 20% of the patients who die do so in the disease-free state, and that the cost of full course of treatment is incurred for every patient who experiences disease progression.*

a) In sheet 'Arm 1', a new column, AR was inserted. AR8 = 'Newly Progressive'. Input cell AR7 = 0.20, AR10 = 0. The cell AR12 =IF((AL10-AL11-(AM10-AM11)*$AR$7)<0,0,AL10-AL11-(AM10-AM11)*$AR$7) and extend the formula up to cell AR370. AR371 =SUM(AR10:AR370).
b) Input BP10 =(BP$2*BP$5*(1-BP$7)+BP$2*BP$6)*IF($A11<BP$3,0,1)*IF($A11<=BP$4,1,0) and extend up to BP369. Cell BP370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BP10:BP369)/$AQ$371) and cell BP371 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BP10:BP369)).
c) Input BR10 =(BR$2*BR$5*(1-BR$7)+BR$2*BR$6)*IF($A11<BR$3,0,1)*IF($A11<=BR$4,1,0) and extend up to BR369. Cell BR370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BR10:BR369)/$AQ$371) and cell BR372 =(BR5+BR6)*BR2.
d) Input BY10 =(BY$2*BY$5*(1-BY$7)+BY$2*BY$6)*IF($A11<BY$3,0,1)*IF($A11<=BY$4,1,0) and extend up to BY369. Cell BY370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BY10:BY369)/$AQ$371) and cell BY372 =(BY5+BY6)*BY2.
e) Input BZ10 =(BZ$2*BZ$5*(1-BZ$7)+BZ$2*BZ$6)*IF($A11<BZ$3,0,1)*IF($A11<=BZ$4,1,0) and extend it up to BZ369. Cell BZ370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BZ10:BZ369)/$AQ$371) and cell BZ372 =(BZ5+BZ6)*BZ2.
f) Input CA10 =(CA$2*CA$5*(1-CA$7)+CA$2*CA$6)*IF($A11<CA$3,0,1)*IF($A11<=CA$4,1,0) and extend it up to CA369. Cell CA 370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CA10:CA369)/$AQ$371) and cell CA372 =(CA5+CA6)*CA2.
g) Input CB =(CB$2*CB$5*(1-CB$7)+CB$2*CB$6)*IF($A11<CB$3,0,1)*IF($A11<=CB$4,1,0) and extend it to CB369. CellCB370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CB10:CB369)/$AQ$371) and cell CB372 =(CB5+CB6)*CB2.
h) Input CC10 =(CC$2*CC$5*(1-CC$7)+CC$2*CC$6)*IF($A11<CC$3,0,1)*IF($A11<=CC$4,1,0), Cell CC370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CC10:CC369)/$AQ$371) and cell CC372 =(CC5+CC6)*CC2
i) Input CD10 =(CD$2*CD$5*(1-CD$7)+CD$2*CD$6)*IF($A11<CD$3,0,1)*IF($A11<=CD$4,1,0) and extend it up to

CD369. Cell CD370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CD10:CD369)/$AQ$371) and cell CD372 =(CD5+CD6)*CD2

j) Insert 4 new columns next to CT; CU, CV, CW, CX. CU8 = 'Alternative prog disease drug acquisition cost 8 months', CV8 = 'Alternative prog disease drug acquisition cost 4 month', CW8 = 'Alternative prog disease drug acquisition cost 1 months', CX8 = 'Alternative Total'.

k) Input CU10 =$AR10*SUM($BP$372,$BQ$372,$BR$372), CU11 =$AR11*SUM($BP$372,$BQ$372,$BR$372)+$AR10*SUM($BP$372,$BQ$372,$BR$372), CU12 =$AR12*SUM($BP$372,$BQ$372,$BR$372)+SUM($AR10:$AR11)*SUM($BP$372,$BQ$372,$BR$372) and extend this formula up to CU369.

l) Input CV10 =$AR10*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372), CV11 =$AR11*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372)+$AR10*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372), CV12 =$AR12*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372)+SUM($AR10:$AR11)*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372) and extend this up to CV369

m) Input CW10 =$AR10*SUM(BS372,BT372,BU372,BV372,BW372,BX372,CE372,CF372,CG372,CH372,CI372,CJ372,CK372,CL372,CM372,CN372,CO372,CP372) and extend this up to CW369.

n) Input CX10 =SUM(CU10:CW10) and extend the formula up to CX369.

o) Input CY10 =CY9+(CX10*$H10*$C10) and extend it to CY369. Input CY370 =MAX(CY9:CY369)

p) The same changes were replicated in sheet 'Arm 3'.

4. *EAG Additional Scenario 4: Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (20% of the patients who die do so in the disease-free state).*

   In this scenario, additional scenarios 1 and 4 are applied together to the EAG base case.

5. *EAG Additional Scenario 5: Alternative approach to calculating the cost of subsequent therapy. Assume that 5% of the patients who die do so in the disease-free state, and that the cost of full course of treatment is incurred for every patient who experiences disease progression.*

This scenario is identical to additional scenario 4, except that cell AR7 = 0.05.

6. *EAG Additional Scenario 6: Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (5% of the patients who die do so in the disease-free state).*

In this scenario, additional scenarios 2 and 6 are applied together to the EAG base case.

7. *EAG Additional Scenario 7: Change PFS reference and 2-step NMA (Generalized gamma)*

In the ‘Input_Efficacy_PFS’ sheet, change cell B9 from ‘Log-logistic’ to ‘Generalised Gamma’.

8. *EAG Additional Scenario 8: Change OS reference and 2-step NMA (gamma)*

In sheet ‘Input_Efficacy_OS’, sheet, change cell B9 from ‘Log-logistic’ to ‘Gamma’.

9. *EAG Additional Scenario 9: Apply Generalized gamma distribution for ‘PFS Parametric distribution for reference curve’ and gamma distribution for ‘OS Parametric distribution for reference curve’.*

In the ‘Input_Efficacy_PFS’ sheet, change cell B9 from ‘Log-logistic’ to ‘Generalised Gamma’.

In sheet ‘Input_Efficacy_OS’, sheet, change cell B9 from ‘Log-logistic’ to ‘Gamma’.

10. *EAG Additional Scenario 10: Alternative utility values for PFS/OS from Nafees et al (2008).*

In the ‘Input_Efficacy’ sheet, change cell C6 from ‘EMPOWER Lung 3 trial, EORTC to EQ-5D-5L mapping (UK tariff, modelled average)’ to ‘Nafees et al (2008), UK tariff (scenario in TA584)’.

11. *EAG Additional Scenario 11: Alternative utility values for PFS/OS from Chouaid et al. (2013), UK tariff (scenario in TA 584)*

In the ‘Input_Efficacy’ sheet, change cell C6 from ‘EMPOWER Lung 3 trial, EORTC to EQ-5D-5L mapping (UK tariff, modelled average)’ to ‘Chouaid et al. (2013), UK tariff (scenario in TA584)’.

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